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The American Heart Journal

VOL. V APRIL, 1930 NO. 4

Original Communications

THE IMPORTANCE OF DIFFERENCES IN THE POTENCY OF DIGITALIS IN CLINICAL PRACTICE*

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NEW YORK, N. Y.

ABOUT twenty years ago Hatcher and Baily[1] compared the doses of one of the digitalis bodies as recommended by different authorities and found a variation in potency as great as 750 times between the largest and smallest dosage. When one considers, therefore, the conditions that prevailed before the advent of the biological methods of assay of digitalis, when there was no way for the physician to determine in advance whether a specimen was active or inert, to say nothing of determining relative degrees of activity, one will indeed appreciate the progress that has since been made. The following recent experience in this matter is significant. A few years ago studies on digitalis dosage were undertaken in the Adult Cardiac Clinic of Bellevue Hospital, and the plan was made to compare specimens of widely different activity. There was no difficulty in obtaining very active specimens of the crude digitalis leaf on the market, but none of low activity was readily available. It was only after the examination of a large number of specimens that one was found with a potency as low as 140 milligrams to the cat unit. From this example one may perhaps overestimate the advance that has been made, but it indicates nevertheless, that the average specimen of digitalis leaf on the market is quite active and, since the U. S. Pharmacopoeia directs a fixed activity (with a limited range) for the official digitalis, the physician is fairly certain to obtain potent digitalis if the specimen complies with the requirements of the U. S. Pharmacopoeia. This progress must be attributed in a large measure to the general application of bio-assay of the drug. The more recent literature dealing with digitalis dosage has become more intelligible because, while dosage has continued in most instances to be expressed in units of weight or measure, the potency of

*From the Third (New York University) Medical Division of Bellevue Hospital and the Department of Pharmacology of Cornell University Medical College.

the specimens is frequently stated, affording in this way some basis of comparison of the experience of different workers. The Cardiac Clinics of the New York Tuberculosis and Health Association have adopted the plan of dispensing digitalis tablets in terms of their activity (cat units) rather than weight, though the equivalent in weight is stated.

It is perhaps quite generally appreciated among physicians that the bio-assay of digitalis is an important determination but it is well known that the average physician makes little use of the data thus obtained, and an examination of the literature reveals the fact that at the present time there is a great deal of misunderstanding in regard to what use the physician should make of the results of this procedure. The need for accurate knowledge regarding the strength of digitalis was called to our attention with great force by the experience of the Committee* for the study of digitalis in pneumonia at Bellevue Hospital. In this communication† an effort is made to clarify some of the issues involved in the application of the bio-assay of digitalis to clinical practice, based upon some of the results obtained by this Committee as well as upon the studies on digitalis dosage in the Adult Cardiac Clinic, both of which will be reported in detail at another time.

Only those facts regarding the work of the Committee necessary for the present analysis will be considered in this report which involves a comparison of some of the data obtained with two preparations of digitalis used in a series of 248 patients with pneumonia.

Two commercial preparations of dried digitalis leaf were used. According to the statements on the labels, one, specimen "A," contained 100 milligrams per cat unit and the other, specimen "B," contained 65 milligrams per cat unit. These statements of potency were at first assumed to be correct and the doses were calculated and administered on that basis. Specimen "A" was dispensed in the form of compressed tablets only; Specimen "B," partly in tablets and partly in capsules that are supplied by the manufacturer.

Table I shows the general plan of dosage employed in the study. At first patients were divided into three weight groups of 125, 150, and 175 pounds respectively. The full dose for each group was calculated on the basis of approximately 0.15 cat unit per pound of body weight, so that the patients in the three groups were to receive a total dose of 18, 22, and 26 cat units respectively. The actual quantities of the drug by weight as seen in the table were smaller for the stronger than for the weaker preparation. The total quantity for each patient was divided into fractions of 30, 30, 15, 15, and 10 per cent respectively

*The Committee was composed of representatives of the First (Columbia University) Medical Division, the Second (Cornell University) Medical Division and the Third (New York University) Medical Division of Bellevue Hospital.

†A preliminary discussion of this subject has been published in the J. A. M. A. 94: 626, 1930.

and given at six hour intervals so that the full dose was administered in about twenty-four hours. If no toxic symptoms appeared a daily maintenance dose of two cat units was then continued. In the course of the work it became necessary for reasons that we shall presently see to reduce the size of the full dose (the smaller dose method of Table I)

TABLE I

SHOWING TOTAL DOSES OF DIGITALIS FOR PATIENTS OF DIFFERENT WEIGHT GROUPS CALCULATED ON BASIS OF POTENCY STATED BY THE MANUFACTURER

METHOD AND PREPARATION	TOTAL DOSES		
	AVERAGE 125 LB.	AVERAGE 150 LB.	AVERAGE 175 LB.
Larger dose method	(18 C. U.)	(22 C. U.)	(26 C. U.)
Specimen "A"	1.80 Gm. (27 gr.)	2.20 Gm. (33 gr.)	2.60 Gm. (39 gr.)
Specimen "B"	1.20 Gm. (18 gr.)	1.47 Gm. (22 gr.)	1.73 Gm. (26 gr.)
	BELOW 150 LB.	ABOVE 150 LB.	
Smaller dose method	(10 C. U.)	(12.5 C. U.)	
Specimen "A"	1.00 Gm. (15 gr.)	1.25 Gm. (18.75 gr.)	
Specimen "B"	0.66 Gm. (10 gr.)	0.83 Gm. (12.5 gr.)	

(C. U.) Cat Units.

TABLE II

SHOWING TOTAL DOSES OF DIGITALIS ACTUALLY RECEIVED BY PATIENTS IN DIFFERENT WEIGHT GROUPS ON THE BASIS OF THE TRUE POTENCY

METHOD AND PREPARATION	TOTAL DOSES		
	AVERAGE 125 LB.	AVERAGE 150 LB.	AVERAGE 175 LB.
Larger dose method	18 C. U.	22 C. U.	26 C. U.
Specimen "A"	(1.8 Gm. or 27 gr.)	(2.2 Gm. or 33 gr.)	(2.6 Gm. or 39 gr.)
	36 C. U.	44 C. U.	52 C. U.
Specimen "B"	(2.4 Gm. or 36 gr.)	(2.94 Gm. or 44 gr.)	(3.46 Gm. or 52 gr.)
	BELOW 150 LB.	ABOVE 150 LB.	
Smaller dose method	10 C. U.	12.5 C. U.	
Specimen "A"	(1.0 Gm. or 15 gr.)	(1.25 Gm. or 18.75 gr.)	
	20 C. U.	25 C. U.	
Specimen "B"	(1.32 Gm. or 20 gr.)	(1.66 Gm. or 25 gr.)	

and only two weight groups were then considered, those under 150 pounds receiving 10 cat units and those above 150 pounds receiving 12.5 cat units. These doses were administered in fractions of 50, 25, and 25 per cent of the total respectively, twelve to eighteen hours elapsing between the first and second dose, and six to eight hours between the second and third dose. A daily maintenance dose of 2 cat units was then administered as in the first method.

Table III shows the incidence of toxic symptoms with the two preparations of digitalis. By the larger dose method, vomiting occurred in only 3.7 per cent of the patients receiving specimen "A" as against 38.4 per cent of those receiving specimen "B". Similarly only 4.9 per cent of the former developed the higher grades of heart-block as against 14.9 per cent for the latter. The total number of patients in

the group receiving digitalis by the smaller dose method is too small to draw conclusions from it by itself; nevertheless, it bears out the results obtained with the larger dose method, namely, a relatively greater incidence of toxic phenomena with specimen "B".

TABLE III

SHOWING INCIDENCE OF TOXIC PHENOMENA WITH THE TWO PREPARATIONS OF DIGITALIS

METHOD	SPECIMEN	TOTAL NUMBER PATIENTS	NO. OF PATIENTS AND INCIDENCE OF TOXIC EFFECTS		
			VOMITING	FIRST STAGE BLOCK ONLY	SECOND, THIRD, FOURTH STAGES BLOCK
Larger dose	"A"	82	3 (3.7%)	23 (28.0%)	4 (4.9%)
Larger dose	"B"	125	48 (38.4%)	33 (26.4%)	18 (14.4%)
Smaller dose	"A"	11	0 (0.0%)	1 (9.1%)	0 (0.0%)
Smaller dose	"B"	30	6 (20.0%)	8 (26.7%)	3 (10.0%)

TABLE IV

SHOWING THE NUMBER OF DOSES ADMINISTERED BEFORE VOMITING WITH THE TWO SPECIMENS OF DIGITALIS

SPECIMEN	"A"		"B"	
NUMBER OF DOSES OF DIGITALIS	NUMBER OF PATIENTS WITH LARGE DOSE METHOD	NUMBER OF PATIENTS WITH SMALL DOSE METHOD	NUMBER OF PATIENTS WITH LARGE DOSE METHOD	NUMBER OF PATIENTS WITH SMALL DOSE METHOD
1	0	0	0	0
2	2	0	17	0
3	0	0	5	0
4	0	0	1	2
5	0	0	20	0
6	0	0	2	0
7	0	0	1	2
8	0	0	1	1
9	0	0	0	0
10	0	0	0	1
11	1	0	1	0

There can be no question that the greater incidence of toxic phenomena with specimen "B" was due to the systemic action of the drug. When vomiting appeared the drug was discontinued, but, as seen in Table IV, at least two-thirds of the total dose had been administered before vomiting occurred. The types of patients in the groups receiving the different specimens of digitalis were fairly comparable, about forty per cent of each being represented by the Pneumococcus Types II and III. The incidence of symptoms similar to the toxic phenomena in large groups of untreated controls was practically negligible.* The relatively greater systemic toxic action of this specimen of digitalis was further confirmed by the relatively greater incidence of the higher grades of heart-block.

*These matters will be discussed in detail in subsequent reports of the Committee.

DISCUSSION

Although the essentials of the present discussion refer also to other methods of digitalis assay, we shall speak in terms of the cat method in order to be more concrete, and because more experience has been

TABLE V

SHOWING INCIDENCE OF VOMITING IN DIFFERENT WEIGHT GROUPS WITH SPECIMEN "B"

WEIGHT GROUPS	LARGER DOSE METHOD		
	AVERAGE 125 LB.	AVERAGE 150 LB.	AVERAGE 175 LB.
Total doses*	36 C.U.	44 C.U.	52 C.U.
Total no. patients	48	67	10
Number vomited	21	21	6
Incidence of vomiting	43.8%	31.3%	60%
WEIGHT GROUPS	SMALLER DOSE METHOD		
	BELOW 150 LB.	ABOVE 150 LB.	
Total doses*	20 C.U.	25 C.U.	
Total no. patients	20	10	
Number vomited	4	2	
Incidence of vomiting	20%	20%	

*On basis of corrected potency.

recorded regarding the application of cat units to clinical use of the drug than of any other biological units. Two distinct principles are involved in the bio-assay of digitalis by the cat method. First, the average normal cat requires a fairly fixed quantity of a given specimen of digitalis per unit of body weight to cause death. Variations are always present, and occasionally very marked, but with a uniform technique satisfactory averages can be obtained. Second, differences in activity of different digitalis preparations can be detected by this method. Both principles have been applied to man, which in turn has given rise to the question as to whether they are true for man and to what extent they are practical.

Eggleston[2] found that when he digitalized a group of patients with a number of digitalis preparations of different cat unit strengths, the doses proved to be most uniform when expressed in terms of cat units per pound of body weight. He did not state that this method would yield the exact dose for any single individual. He showed, as many others have also seen, that there are marked variations in the doses for different patients, but that the range of variation was wider when the doses were expressed as total quantity per patient than when expressed as cat unit per pound of body weight. In a recent study Martin[3] confirmed the relationship between total dosage, the body weight of patients, and the biological activity of different specimens of digitalis. Scores of workers have availed themselves of that technique and have thereby popularized the large dose method of administering digitalis. It is necessary to bear in mind that both principles are here involved; (1) that body weight is a factor in digitalis dosage, and

(2) if one specimen is found to be more active than another in cats, it will also be found more active in man.

Some authors have questioned the validity of these conclusions and some, their practical value. H. J. Stewart[4] recently made the following statements: "Experience has shown that the biologic assay of the drug (digitalis) by the cat or by the frog method does not parallel the therapeutic effect in patients. The amount, however, of any preparation that is required to give this effect is approximately the same regardless of the age and the weight of the patient." There are no potent drugs in the materia medica that one would venture to give to patients of five or six years of age, or to those weighing forty or fifty pounds, in the same doses required for full effects in adults weighing 150 to 175 pounds. When digitalis, like any other drug, enters the circulation, it is distributed throughout the entire body and is taken up by many tissues, only a fraction of the total reaching the heart. Hence if one patient weighs twice as much as another, the same dose will result in a smaller allotment for the heart.

The principle that body weight and dosage are related simply expresses the idea that a very small man will require less digitalis than a very large man to produce a given effect, other conditions being the same. In actual practice, these other conditions are usually not found to be the same. This merely places a limitation on the value of the weight factor, since there are many variables to be dealt with in the treatment of heart disease, among which body weight is only one. For example, the average ambulatory cardiac patient usually does not require the same degree of digitalization found necessary for the average patient in acute congestive heart failure, and even though these two patients may be of the same weight, a difference in their degree of failure may make it necessary to give one much larger doses of digitalis than the other.[5] The nearer the weights of patients approach each other between such extremes as mentioned above, the less apparent does the weight factor become. The counterplay of the many variable factors makes it a matter of some difficulty to estimate the rôle of any one, and under such conditions a few studies confirming a sound principle are probably more nearly correct than a number that fail to do so. An interesting indication of the body weight factor is seen in Table V, in which the patients of the pneumonia series were distributed into groups according to weight in order to determine the incidence of vomiting in each. The number of patients in the 175 pound group is too small to be considered. Of the patients in the 150 and 125 pound groups, the former or heavier, received twenty-two per cent more digitalis than the latter or lighter group. If no relationship between body weight and dosage exists among adults, the group which received more digitalis would have shown a greater incidence of vomiting. Our justification for the assumption that the effect of a

twenty-two per cent greater dose could be detected is the fact that the patients in the lighter group were already receiving a rather toxic dose, namely, one after which nearly one-half of the patients vomited. The results do not show a greater incidence of vomiting in the heavier group, favoring, therefore, the probability that the body weight was a factor in the dosage. There can be little question that under suitable conditions body weight can be shown to be a factor in digitalis dosage as in that of any other potent drug. If one attempts to use the body weight factor to determine differences in the amount of digitalis required by a patient of 130 pounds with arteriosclerotic heart disease showing mild signs of heart failure and that by a young patient of 150 pounds with rheumatic heart disease showing acute congestive heart failure, there can be little surprise if one detects no relationship whatsoever between dosage and body weight. The value of using the factor of body weight in estimating dosage has been obscured by those who have attempted to employ it as a fixed rule of thumb, as a substitute for, rather than as a helpful guide to, the principle of dosage which is, in the last analysis, to give enough to produce full therapeutic effects and not so much as to produce toxic effects.

The second principle relating to biological activity of digitalis is more important from the practical standpoint. Stewart stated that the biological assay of digitalis does not parallel the therapeutic effect in patients, and that of a commercial specimen, digitan, which he has used for years, one gram given by mouth within twenty-four hours usually produces satisfactory full digitalization. Let us now ask how his experience can be translated into terms intelligible to those who do not use digitan. Is his experience different from that of scores of other workers who have found that it requires about one and one-half to two grams of active digitalis to produce full effects, or is it the same, the differences in the quantities stated being due merely to differences in activity of the preparations used? There is no way of knowing from his report, because digitan is assayed by the frog method of Gottlieb, a method not official in the U.S. Pharmacopoeia and not in common use in this country, and no satisfactory data are available for translating these into cat units or standard frog units of the U.S. Pharmacopoeia. Furthermore, there is no assurance that digitan is of constant activity because the method of Gottlieb does not require the standardization of frogs, the susceptibility of which is known to vary considerably. As it stands, therefore, the dosage of digitalis given by Stewart differs from that of many other observers, but it is not possible to know whether or not a new fact has been uncovered, because in a sense, the different authors do not speak the same language.

From all facts at present available, it would be sound to assume that if one specimen of digitalis is twice as active as another when it is

brought into contact with the cat's heart at a given rate, the same relative activity between the two would be present in man (though not necessarily the same absolute activity) under similar conditions. But since the drug is usually given by mouth in man, the factors of absorption and elimination complicate the determinations of the relative activity of any two preparations. Obviously when two specimens of digitalis have the same activity, but differ in rate of absorption and elimination, their dosage may be different. This simply places a theoretical limitation on the value of bio-assay by the cat method, and makes it necessary to bear in mind that if one specimen is twice as active as another by intravenous injection into the cat, it may not necessarily be twice as active by oral administration in man. But in actual practice, barring the occasional specimen of digitalis that is poorly absorbed, one finds that preparations with significant differences in biological activity by the cat method reveal these differences when used in man, if suitable conditions are present to detect them. Patients can often tolerate much larger doses of digitalis than are necessary to maintain a condition of optimum improvement.[5] It is in this range between the minimum necessary dose and the maximum tolerated dose that moderate differences in biological activity of digitalis escape notice in clinical practice. This again does not vitiate the practical value of biological assay. A more vigorous method of digitalis dosage, on the contrary, shows the indispensability of an accurate knowledge of the relative potency of digitalis preparations, as was illustrated by the experience of the Pneumonia Committee. As already stated, two well-known commercial specimens of digitalis leaf were employed, one about fifty per cent more active than the other, according to the labels of the manufacturers The toxic symptom, vomiting, occurred in more than ten times as many patients with that specimen which was given in smaller doses in terms of grains (specimen "B") although a uniform technique was employed and comparable doses of the two preparations were given in terms of their supposed potency. This, on the surface, seemed to support Stewart's statement that biological assay does not parallel the therapeutic effect in patients. The two specimens were then tested by the cat method in the Department of Pharmacology of Cornell University Medical College. The results showed that the tincture of specimen "A" had the potency stated on the label, namely, one c.c. per cat unit, while the tincture of specimen "B" was found to have a potency of about 0.4 c.c. instead of 0.65 c.c. per cat unit. The latter tincture was tested independently by the cat method in the Department of Pharmacology of the University of Michigan and the results agreed with those obtained at Cornell, namely, that the tincture of specimen "B" was about sixty per cent more active than was stated by the manufacturer. The tablets of specimen "B" were then examined biologically, and this resulted in the discovery that each tab-

let did not represent one cat unit as stated on the label, but two cat units. Hence, the tablets of specimen "B" were 100 per cent stronger than the statement by the manufacturer indicated. Since the tablet contained some inert matter it was impossible to state whether the greater strength of each tablet was due to a greater potency of the digitalis leaf itself, or whether each tablet simply contained two grains of digitalis instead of one.

With these facts in hand the total doses of specimen "B" that were received by the pneumonia patients were recalculated. These are shown in Table II. While it was at first believed (see Table I) that the patients were receiving comparable doses of the two preparations, the results in Table II show that on the basis of the true potency, those treated with specimen "B" actually received twice as much digitalis as those with specimen "A", and this accounted for the high incidence of toxicity with the former preparation. A more suitable example could hardly be found that shows the close parallelism existing between the cat method of bio-assay of digitalis and the effects in man. An erroneous statement regarding the cat unit potency was promptly detected in the form of toxic symptoms in patients when comparatively large doses of digitalis were used. If very small doses had been used, it is indeed probable that the misstatement of the manufacturer regarding the activity of the drug would have escaped detection.

This brings us to a related matter about which a better understanding is necessary. Levy and Mackie[6] in a recent paper advocated the use of "standardized digitalis" and stated the average full dose to be about 1.5 grams under certain conditions. The word "standardized", however, does not have a fixed meaning, the U.S. Pharmacopoeia having one standard and the various manufacturers having their own standards. The importance of these differences in standards may be seen from the following example. Each of two well-known commercial specimens of digitalis are referred to on the labels as "standardized", yet one is stated to have a cat unit strength of 100 milligrams, and the other a cat unit strength of 65 milligrams. The question at once arises to which, if any, of these preparations does the statement of Levy and Mackie refer, in which they say that 1.5 grams is the average full dose of "standardized digitalis", since one of these so-called "standardized" preparations may contain about one and one-half times the activity of the other in the 1.5 gram dose. Another commercial specimen of digitalis which has proved to be quite active merely bears the label "physiologically tested" as if the results of that test were of interest only to the manufacturer. The condition is somewhat analogous to a physician sending a specimen of blood for a urea determination and finding that the only report available is that the determination has been made. Physiological testing is essentially a quantitative determination, not so much to ascertain whether a given preparation has digitalis action as to determine by how

much one specimen is stronger than another. Compliance with the requirements of the U.S. Pharmacopoeia does not in itself insure sufficient uniformity in strength for accurate clinical studies because two specimens of digitalis may meet the official requirements and yet one may be as much as thirty per cent more active than another by the frog method. Again it is necessary to emphasize what we have already stated, that under many conditions these differences in the potency of digitalis may escape detection in practice, but where large doses are necessary a knowledge of these differences will avoid a great deal of unsatisfactory use of the drug in the nature of excessive or insufficient digitalization.

There are many points of similarity between the problem of the dosage of digitalis and that of insulin. Both drugs vary in activity and are assayed biologically. No one would doubt that it is irrational to speak of insulin dosage in terms of c.c. without naming the standard, because one c.c. of insulin may contain 20, 40, or 80 units. Nevertheless, it is common practice to refer to the dosage of the tincture of digitalis in terms of c.c. without stating the potency, though it is equally irrational because a c.c. of one specimen of the tincture may represent one cat unit, while that of another specimen may represent two or more cat units.

Finally, it is necessary to call attention to the question of the bearing of the biological strength of digitalis upon the relative merits of different preparations. Obviously, in order to be of therapeutic value, digitalis must be active. But the views commonly held that one digitalis preparation is better than another because one is 25 or 50 per cent, or even 100 per cent, more active than another, does not display a sufficient sense of relative values. There are preparations of digitalis on the market of which the sole claim to superiority is a fifty per cent greater activity as determined by bio-assay. The only possible advantage of a more active specimen from a therapeutic standpoint would be the diminished bulk of the individual doses. If the biological assay shows one preparation to be weaker than another within reasonable limits (differences of as high as 100 per cent are not commonly seen), it is of course necessary to give a larger quantity of the weaker preparation. What possible difference does it make, however, whether a patient receives a daily dose of two grains of the stronger or so-called "good" preparation instead of a dose of three or four grains of the weaker or so-called "poor" preparation? Since digitalis is a potent drug, the dosage of which is measured in quantities of grains, and not ounces or pounds, bulk can rarely be a matter of any importance, and the fact that a few additional grains may be necessary in the case of the weaker preparation affords no reasonable objection to it. The general interest in the question of "stronger" and "weaker" preparations has only served to obscure the significance of the fact that it is a matter of no

importance whether one preparation is stronger or weaker than another (within reasonable limits), provided one knows the exact potency of each.

SUMMARY

1. This communication deals with an analysis of the factors involved in the application of the bio-assay of digitalis by the cat method to clinical practice.

2. Evidence is presented showing that body weight is a factor in digitalis dosage and that it is essential to take into account differences in potency of digitalis as determined by bio-assay.

3. It is pointed out that when small doses of digitalis are used, the value of both factors (body weight and differences in potency) may escape detection.

4. An analysis is made of the experience of the Committee for the study of digitalis in pneumonia at Bellevue Hospital with a well-known commercial preparation of digitalis, the potency of which was later proven to have been incorrectly labelled by the manufacturer. This analysis shows in the first place, that a specimen of digitalis which was found to be about twice as active as anticipated for man proved to be also twice as active by the cat method of assay; and secondly, it shows the dangers arising from the use of digitalis, especially in large doses, without knowing the exact potency.

5. Evidence is presented showing the confusion which arises from the use of the term "standardized digitalis" without stating the exact potency because of the different standards used by the various manufacturers.

6. The relative merits of so-called "stronger" and "weaker" preparations of digitalis are discussed.

REFERENCES

1. Hatcher, R. A., and Baily, H. C.: Tincture of Strophanthus and Strophanthin, J. A. M. A., **52**, 5, 1909.
2. Eggleston, C.: Digitalis Dosage, Arch. Int. Med., **16**, 1, 1915.
3. Martin, L. E.: A Clinical Standardization of Digitalis, J. Pharm. and Exp. Therap., **31**, 229, 1927.
4. Stewart, H. J.: The Objects of Digitalis Therapy, THE AMERICAN HEART JOURNAL, **5**, 1, 1929.
5. Gold, H., and De Graff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients. I. The Use of Digitalis in the Cardiac Clinic, J. A. M. A. **90**: 1016, 1928.
6. Levy, R. L., and Mackie, T. T.: The Drug Treatment of Heart Disease, J. A. M. A., **89**, 432, 1927.

TWO CASES OF COMPLETE OCCLUSION OF BOTH CORONARY ORIFICES*

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IT IS now generally conceded that of all the smaller vessels of the body whose function is necessary to the continuation of life none are more essential than the coronary arteries. The sudden dramatic termination of life which so frequently results from the occlusion of a branch of a coronary artery furnishes ample support for this thesis. Death from coronary obstruction may be and frequently is the most sudden form of death known. A man may literally drop dead. So characteristic is the manner of death that a usually successful snap diagnosis may be made from that evidence alone. Deaths from cyanide poisoning and those occurring in certain cases of hypertensive heart disease with edema of the brain, practically alone rival coronary occlusion in the rapidity with which death may be produced. (Sudden deaths from aortic insufficiency, in which the coronary orifices are not occluded, are due to interference with the coronary blood supply, in our opinion.)

On the other hand, it is well known that extensive lesions of the coronary arteries may exist for long periods of time without manifest debilitating effect and even without any clinical signs or symptoms whatsoever. There are many cases on record where the fatal occlusion of the artery led to the first suspicion of the presence of coronary disease.

As medical examiner of Suffolk County, one of us (T. L.) is called upon to investigate deaths of human beings, supposedly due to violence. This term has been interpreted to include deaths in which the causation is not apparent or adequate. Under this provision there come under the jurisdiction of the medical examiner a number of cases in which investigation discloses that death was due to natural causes or disease. As is to be expected this group embraces a considerable percentage of sudden deaths in which the cardiac circulation is at fault.

Among the cases of this character seen in recent years are the following two, in which there was essentially complete obliteration of both coronary orifices.

*From the Medical Examiner Service of Suffolk County and the Boston City Hospital.

CASE REPORTS

CASE 1.—J. B., Swedish male, white, thirty-five years old, had been in America for eighteen years. His principal occupation had been that of a sailor. His uncle who brought him to this country complained that he never stuck to any job for a long time. During intervals between sailings he had worked off and on for a local awning company as an extra man. The work of this company is seasonal, awnings being put up in the spring and taken down in the fall. He had been out of work much of the winter of 1925-1926, not because of illness, but because of difficulty in getting work. He worked for the awning company from April 30 to August 5, 1926, and was then laid off with other extra men. He was employed again October 5 and worked until November 5 when extra work stopped for the year. During this latter period he worked five or six days per week. He was seen by his uncle two weeks before his death, at which time he had a cold and looked badly. He told his uncle he had been carrying heavy awnings and awning rods in the rain and had caught cold. His uncle stated that he had a "raving" appetite and ate too much. As a result he had "stomach trouble—indigestion." He had suffered from headaches for years. He did not drink but smoked many cigarettes. He had not been treated by a doctor since he came to this country.

He roomed in a lodging house and was last seen alive November 10, 1926, at 7 A.M. He was found dead in bed by his landlady on November 11 at 1:30 P.M. When found, he was clothed, though in bed, in a wool sweater over a cotton union suit and with a khaki wool scarf wound about his waist. From the appearance of the body it was evident that death had occurred probably twenty-four hours or more before its discovery.

At the post-mortem examination the heart cavities contained gas and frothy fluid blood which was hemolized. Smears furnished abundant gram-positive bacilli, with B. welchii morphology. Heart and aorta showed some staining of surfaces with blood coloring matter. Each pleural cavity contained a fluid stained with blood coloring matter, the right 225 c.c. the left 150 c.c. The long delay in the discovery of the body, which was covered with excess clothing, had evidently favored the post-mortem incubation of B. welchii.

The pathological findings of interest were confined to the heart and aorta. Otherwise nothing remarkable was found.

The pericardium was smooth and lustrous, containing 5 c.c. of blood-tinged fluid.

Heart weighed 328 grams. The heart muscle was flabby, gray red. Wall of left ventricle measured 1.4 cm.; wall of right ventricle measured 0.5 cm.; mitral valve measured 8.6 cm.; aortic valve measured 7 cm.; 5 cm. above ring, aorta measured 8.5 cm.; pulmonary valve measured 7.8 cm.; tricuspid valve measured 10.3 cm.; depth of left ventricle measured 7.3 cm.

On section the heart muscle was homogeneous, disclosing no evidence of fibrous tissue.

The ascending arch of the aorta showed a continuous series of irregular masses of raised, nodular, translucent and opaque, gray white tissue encircling the vessel above the ring and extending into the sinuses of Valsalva. This girdle (girdle of Venus?) measured 1.8 cm. in breadth at its narrowest point above the right coronary sinus and extended for 6 cm. above the ring over the left coronary sinus along the region of contact of the aorta with the pulmonary artery. The process of scarring and thickening of the aortic wall extended into the depths of the right coronary sinus to its lowest limit. In the left and noncoronary sinuses the wall was thickened only in the upper part of each sinus, the wall of the noncoronary sinus showing thinning in its lower portion, measuring only 0.1 cm. in thickness.

The site of the orifice of the right coronary artery was occupied by nodular scar tissue without suggestion of the location of the original orifice. The site of

Fig. 1.—Case 1. Drawing of the heart and ascending arch of aorta. Below are drawings of the cross-sections of the left coronary and right coronary respectively, as they are seen from the rear within the aortic wall (enlarged 3 diameters).

the orifice of the left coronary artery was indicated by a shallow dimple. Serial sections through the tissue behind the aortic wall disclosed grossly complete obliteration of the proximal portions of both coronary arteries by a relatively translucent gray tissue. This obliteration extended just through the adventitia of the aorta in either case and stopped abruptly. The coronary arteries beyond this obstruction showed a wall of apparently less than normal thickness. The vessels were of small caliber and were filled with blood.

There was some dilatation of the left ventricle due probably in part to the frothy blood and gas found within the cavity post-mortem. Otherwise, apart from slight thickening of the free edges of the aortic cusps, particularly about the corpora Arantii, the valves and cavities were normal.

The aorta showed in transverse and descending arches few small and larger, slightly raised, gray white nodules. The thoracic and abdominal aorta was thin, smooth and elastic.

The lungs showed a moderate edema.

Microscopical examination of the coronary arteries was carried out by shaving pieces from the back of the aorta. These pieces were then imbedded and sectioned. The actual point of most complete obliteration in each artery was in relation to the intima of the aorta.

Right Coronary Artery.—The lumen of the vessel was obliterated, save for a very small eccentric opening, by young, relatively cellular connective tissue from the subendothelial layer. Through one segment of the media of the coronary artery a collection of vasa vasorum, evidently arising from the adventitia of the aorta, were thrust through the coronary media to enter the young intimal tissue. The media was otherwise not remarkable. In the adventitia and surrounding tissue there was edema with large focal collections of lymphoid and plasma cells, some of which were perivascular. Stains for study of the elastica were unsatisfactory because of poor preservation.

Left Coronary.—Microscopical examination showed obliteration of lumen save for a small opening, eccentric, but less markedly so than in the right coronary. The original lumen was largely filled with old, relatively acellular hyaline and vacuolated connective tissue, particularly about the region of the small vascular opening. Along the wall at either end of the oval contour of vessel, there were considerable collections of round cells in younger connective tissue, with multiple canaliculi. The muscle wall showed marked thinning in one segment, and surrounding tissue contained large collections of round cells.

The heart muscle was normal, without fragmentation or segmentation. There was no increase of connective tissue and no round cell infiltration. The vessels were normal. Sections stained with scharlach r showed no fatty metamorphosis of muscle.

Case 2.—L. F. J., a single colored woman, twenty-six years of age, lived in the rear of a small store owned by her lover. She went out daily as a dressmaker to within a few days of her death. She was said to have had acute indigestion for several days before her death. She was found dead at 1:20 A.M., January 21, 1926, having been last seen alive at 10 P.M., January 20. Investigation later revealed that she had been treated by a local doctor on two occasions in the month preceding her death. She complained to him that she was tired and short of breath. He found a systolic blood pressure of 180-190, diastolic 90-100, with a systolic murmur. The area of cardiac dullness was increased. He made a diagnosis of hypertension.

The woman's lover reported that she had been perfectly well up to two months before her death. She collapsed in the street and since that time had had five similar attacks of "going limp." All but the first attack occurred at night

under sexual excitement. He applied hot fomentations over the breast, and with rubbing she "came to" in a few minutes.

The body was that of a slender, café au lait negress, 5 feet 1½ inches, well developed and nourished; brown eyes, pupils equal, 0.5 cm. The body was fully clothed. There were vomitus and dried froth over neck and left shoulder. Breasts were small and showed large pigmented areola. No contents could be expressed. Fingers were not clubbed.

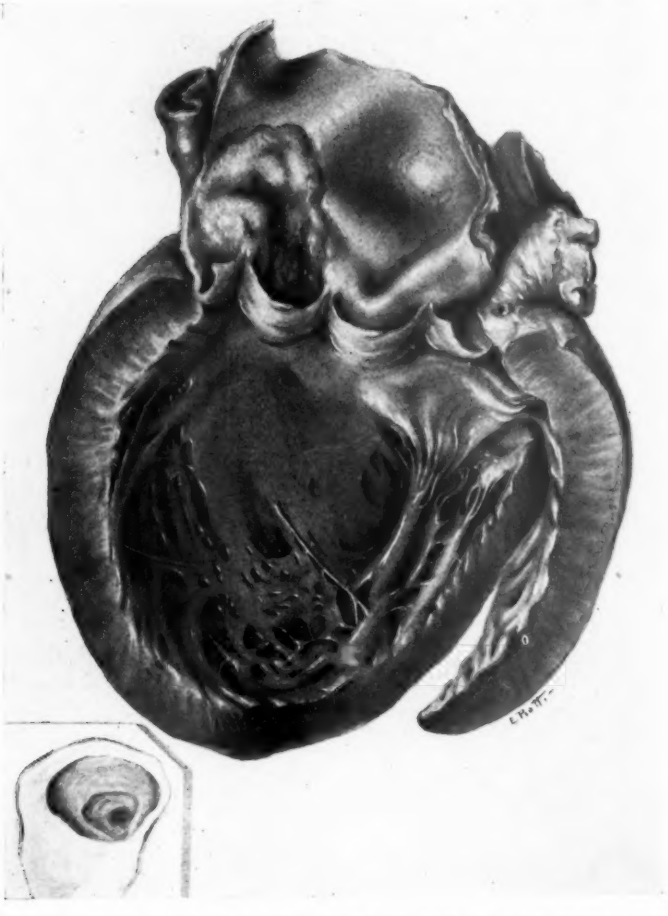

Fig. 2.—Case 2. Drawing of the heart and ascending arch of aorta. Below is a drawing of the cross-section of the right coronary artery as seen from the rear within the aortic wall (enlarged 3 diameters).

As in Case 1 the significant post-mortem findings, apart from an old repaired salpingitis, perisalpingitis and periovaritis, and the occurrence of uterine myomata, were limited to the heart and aorta.

The pericardium was smooth; contained 5 c.c. of a clear serous fluid.

The vessels of the neck and the cavities of the right heart were widely distended with fluid blood and a small amount of lax mixed clot.

The heart weighed 285 grams. The heart muscle was light red, firm, homogeneous.

Heart measurements:

Wall of left ventricle measured 1.2 cm.; wall of right ventricle measured 0.45 cm.; mitral valve measured 8.4 cm.; aortic valve measured 7 cm.; pulmonary valve measured 6.4 cm.; tricuspid valve measured 10.1 cm.; depth of left ventricle measured 7.2 cm.

Valves and cavities were normal.

The arch of the aorta showed a crescentic zone of slightly raised, nodular thickening, incomplete over the noncoronary sinus, extending 3.5 cm. above the ring over the left and the right coronary sinuses. The site of the orifice of the right coronary artery was occupied by smooth scar tissue. In opening the heart the enterotome cut through the left coronary artery near the orifice. Viewed from behind the left coronary was of normal caliber, which narrowed sharply to closure. A slight dimple in the surface of the aorta marked the site of the orifice. The ascending arch apart from these lesions, and a few small pinhead yellow foci were thin and smooth. The aortic cusps showed no thickening or other changes. The aorta below the arch was thin, smooth and elastic.

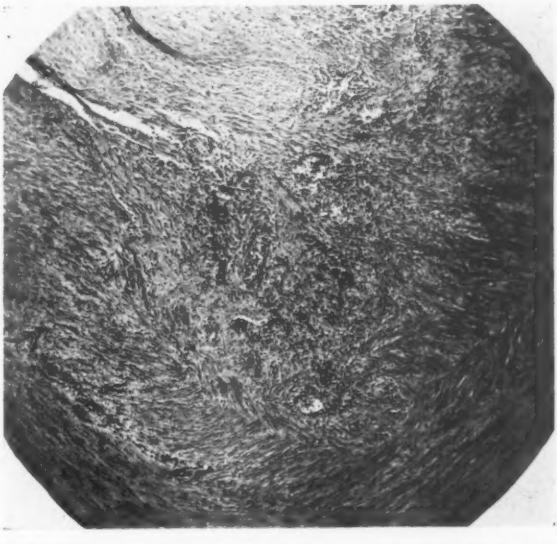

Fig. 3.—Photomicrograph of portion of occluded right coronary artery, Case 2, to show vasa vasorum passing through wall (enlarged 80 times).

Microscopic examination of the right coronary artery in the region of obstruction showed the lumen of the vessel obliterated. Near one end the occlusion was due to an older, more hyaline, and relatively acellular connective tissue. Throughout this tissue, however, were distributed small collections of lymphoid cells, for the most part in rows, with larger collections near the junction of the intima and media. Toward the other end occurred a younger, more cellular, less hyaline, connective tissue containing vessels and exhibiting dense collections of round cells, notably about the vessels. The infiltrating cells were largely lymphoid and plasma cells, with some histiocytes. The vessels were numerous and, except in the vessels of small caliber along the junction with media at one point, bore no resemblance to the irregular clefts converted into vessels which are seen in the canalization of a thrombus. The invading arteries were readily identifiable as such. The muscle coat of the occluded coronary showed in places collections of round cells, particularly about arteries penetrating this layer, and hyaline changes with thickening and

thinning of the muscle coat were apparent along one segment of the vessel wall. The surrounding fatty and connective tissue harbored massive collections of infiltrating cells about blood vessels.

The left coronary artery showed on microscopical examination an abrupt narrowing as it passed through the aortic wall. The lumen of the vessel was distorted and compressed by a high grade edema of the subintimal layer of the intima, associated with the occurrence of fibroblasts, histocytes, and lymphoid and plasma cells. The infiltration with small round cells was more diffuse and more marked in this lesion than in the three other coronaries thus far considered.

After long fixation in Kaiserling with loss of fluid, thinning and retraction of the lesion in the aortic wall, a line representing the lumen of this vessel could be grossly followed through the aortic wall.

DISCUSSION OF THE PATHOLOGY OF THE LESIONS

In most of the forms of obliterative endarteritis of vessels of the size of the coronaries the complete occlusion of the lumen has depended in part upon thrombus formation, early or late, to be followed by organization of the thrombus.

Klotz[1] says that rarely if ever does obliteration of a vessel take place as a result of an internal proliferation simply. He found that the complete occlusion was due to thrombosis. Gurd and Wade[2] describe obliterative lesions in small vessels (less than 1 mm. in diameter) due wholly to proliferation of the intima.

In the physiological obliteration of the ductus arteriosus and the upper portions of the hypogastric arteries, following birth, contraction of the wall, followed by subendothelial growth of the intima rapidly convert the vessels into fibrous cords with minimal thrombosis. Accompanying and following the involution of the uterus and ovaries, a productive endarteritis may arise. But in the latter group thrombosis may be a factor in leading to occlusion of the lumen. In thromboangiitis obliterans and in syphilitic processes in the cerebral or peripheral vessels thrombosis is the standard means of closing the lumen. In the lesions with which our paper deals thrombosis plays no part. The closure of three of the four vessels is dependent upon a progressive increase of the subendothelial layer of the coronary intima which narrows the lumen to such a degree that ultimately it becomes so small that it cannot be differentiated from the vasa vasorum which supply the organizing tissue. These vasa vasorum, supplying the aorta, penetrate through the muscle coat of the coronary arteries and are responsible for the character of the process, which is limited sharply to that portion of the coronary arteries which lies within the aortic wall. This form of obliterative endarteritis is remarkable in that the organizing agencies which obliterate the canal are not dependent upon the powers of the affected vessels but are derived from more potent forces from without the vessel to be occluded. These conditions can practically only obtain in relation to the branches of the aorta as they pass through the aortic wall. The process preserves

the integrity of the endothelium lining the coronary lumen so that thrombosis does not occur. There are no degenerative changes other than hyaline in the subendothelial layer, so that the endothelium is well supported throughout the progress of the disease. There is little distortion and no flattening of the lumen, which is progressively narrowed and modified to accommodate it to new conditions, until ultimately it has shrunk to the dimensions of one of the invading vasa vasorum, from which it cannot be differentiated.

The Degree of Occlusion.—The heart in Case 1 showed grossly complete obliteration of both coronary arteries not only at the orifices but throughout the thickness of the aortic wall. This is also true of the right coronary in Case 2. In the left coronary of this case the occlusion was dependent in considerable part upon edema of the thickened intima of the aorta. Injection of fluid into the coronary arteries behind the aorta in each of these four vessels, after the hearts had been fixed in Kaiserling, resulted in the delivery of no fluid onto the aortic surface. The occlusion was apparently complete. From the nature of the obliterative process, however, which preserves the original lumen, it seemed probable that some fluid should make its way through the small lumen which persisted. An opportunity to test this presented itself in the fresh heart of a third case in which the right coronary orifice alone was obliterated. In this case the right coronary artery was tied 2 cm. from the aorta, and saline solution was injected with some force from behind. Fluid escaped onto the surface of the aorta in drops which formed and broke as though the delivery were from a small vessel. The opening through which the fluid escaped onto the aortic surface was too small to be seen.

The question of the degree of occlusion is from the practical standpoint only academic, however, since it is impossible that a circulation adequate for the needs of the myocardium could be carried on through a vessel the size of a vas vasis.

The Condition of the Heart.—The hearts in these two cases weighed, respectively, 328 and 285 grams. Both weights are perhaps slightly above normal for the individuals, but the measurements are essentially normal. The measurement of the aortic ring in Case 1 bears essentially the normal ratio to the size of the pulmonary ring. The aorta above had begun to dilate, however, whether due to a slight insufficiency of the relatively normal aortic valves, to the aortitis, or to both is a question. In Case 2 there was no evidence of aortic insufficiency, and the arch above the lesion was intact and not dilated.

The circulation to the heart muscle was apparently adequate under ordinary conditions in each case. No evidence of fatty change, active myocarditis or repair was found in either case. The histories indicate that the individuals were comfortable except under condition of stress; overeating in Case 1, sexual or other emotional stimulus in Case 2.

THE LITERATURE OF OBLITERATION OF THE CORONARY ORIFICES

Allbutt[3] says: "Among the hearts which Kanthack examined with me I remember one in particular which was notable in this respect, that not only were the coronary arteries calcified, but their orifices were so utterly obliterated that the very seat of them was undefinable; yet in so far as the microscope could tell us the myocardium was normal." Vaquez[4] cites a case in a youth of eighteen years, complaining of pain in the precordial region, provoked by exertion and extending toward the left shoulder, and in whom, following physical examination, "clinically the diagnosis of organic angina could be excluded." Several days later he died in a paroxysm of pain. "At the autopsy, to our surprise, we found that there was a diffuse aortitis of the ascending portion of the aorta. The lesions predominated in the supra-sigmoid region, where they had caused a sort of puffiness of the internal coat, chiefly about the orifices of the coronary arteries, which, if not obliterated, were at least notably obstructed." Notable obstruction is not occlusion, as a study of a large series of syphilitic aortae demonstrates.

The case mentioned by Cabot[5] does not belong in this group.

An interesting case, not of closure of the coronary orifices but of obliteration of the vessels beyond the orifices, is reported by Rondeau.[6] A man of sixty years, who died of carcinomatosis, primary in the liver, was found at post-mortem examination to show: ". . . . obliteration of both coronary arteries by a cretaceous clot, which follows the principal divisions of the arteries of the heart." He comments: "In the presence of so long-standing alteration of the coronary arteries that it produced complete obliteration of these vessels, it is astonishing that neither were any cardiac disturbances observed during life, nor more extended and pronounced lesions of the cardiac musculature (some fat granules)."

THE CORONARY ARTERIES BEYOND THE AORTA

In the reported cases of coronary orifice occlusion, in which from the age of the patient and description of the lesions it is evident that the occlusion is due to syphilitic aortitis, the comment is practically constant that the coronary arteries beyond the occluded orifices are normal. Even in older individuals in whom one can suspect from the localization of the lesions in relation to the aorta that the original process was syphilitic, it is usual to find reports of normal coronary vessels or those showing only the senile type of sclerosis.

The rarity of syphilitic lesions in the primary coronary arteries and their main branches is one of the interesting peculiarities of this protean disease. The cerebral vessels, of similar caliber, are a favorite site for syphilitic processes, the coronaries rarely so.

The indefatigable Warthin[7] who has made exhaustive search of materials for the purpose of discovering evidence of syphilitic disease, and who found syphilitic processes in the pulmonary, iliac, femoral, popliteal, tibial, carotid and subclavian arteries, says: "Syphilis of the coronary arteries, in our experience, has been found much less frequently than anticipated from its frequent mention in the literature. Although myocardial lesions occur in practically every case of late syphilis, these are interstitial infiltrations and proliferations along the smallest capillaries between the heart muscle fibers, and the larger branches of the coronaries only rarely show lesions that can be recognized as syphilitic. In every case in our experience these have been of the nature of an arteritis with obliterating proliferation of the intima often associated with thrombosis. Secondary arteriosclerotic changes may follow the healing of these lesions, as elsewhere, but the syphilitic nature of the process can only be recognized in the early stages."

Many authorities fail to agree with Warthin about the frequency of syphilitic myocardial lesions, and the type of syphilitic obliteration of the larger branches of the coronary arteries associated with thrombosis has not been found by us.

Scott[8] says: ". . . . it is interesting to note that in spite of the active disease surrounding their orifices the coronary vessels themselves were seldom involved. When opened they presented a smooth normal surface."

Clawson and Bell[9] after discussing the narrowing or closure of the coronary orifices say: "As in the cases of aortic insufficiency coronary disease in these fifteen cases was rare, with the exception of syphilitic involvement of the orifices."

Our constant experience confirms these findings.

THE SUPPLY OF BLOOD TO THE CARDIAC CIRCULATION

It is quite clear in view of the findings that these two people were able to work and go about their daily lives with their coronary arteries completely occluded. The logical question therefore is, how did the heart muscle get sufficient blood supply to enable it to carry on its function efficiently? It is natural to look for additional coronary arteries but none could be found. One is left, therefore, with two possibilities. The first is that a potential source of blood exists in the anastomoses of the vasa vasorum of the aorta; but there was no enlargement of these channels, and, even had there been, it is only too obvious that the amount of blood which could be delivered through these vessels would not furnish blood enough to supply energy for the work of a single auricle. One is left then with the Thebesian veins as the only vessels capable of supplying blood to the muscle.

Vieussens[10] in 1706 showed a connection between the coronary arteries and the heart chambers, and two years later Thebesius[11] demonstrated a communication between the veins and the chambers of the heart. Many others have shown the presence of these vessels since that time, but F. H. Pratt[12] first demonstrated that it is possible to keep a mammalian heart beating by perfusing blood through the Thebesian vessels. His ingenious and conclusive experiments demonstrated for the first time the possibilities of a blood supply from the ventricles directly to the heart muscle. Since Pratt's experiments Crainicianu[13] (1922) has shown that when the coronary arteries were perfused with salt solution most of the perfusate escaped into the chambers of the heart and relatively little escaped via the coronary sinus. Wearn[14] confirmed the work of Crainicianu and found in some instances that as much as 90 per cent of the perfusate injected into the coronary arteries escaped directly into the heart chambers. Moreover, by serial histological sections a direct connection was shown to exist between the Thebesian openings in the ventricles and the veins and capillaries of the heart. Evidence was also brought forward to show a direct connection between the coronary arteries and the chambers of the heart.

With these findings in mind the channel of the blood from the ventricles to the heart muscle in the two cases reported in this paper is obviously through the Thebesian vessels. Nor is it surprising that these vessels are ample in size to supply the heart with a sufficient amount of blood when one examines the results of the experiments of Crainicianu and Wearn.

The histological study of the sections through the occluded area of the coronary arteries in these cases reveals a process of long standing —probably evolved over a period of months or longer. In view of this fact one is surprised to find so little evidence of heart disease in the histories of these patients. These people were able to work, and one of them did heavy work with both coronary arteries closed. It is difficult to devise any experiment that can demonstrate more conclusively the fact that under given conditions the Thebesian vessels can take over the rôle of the coronary arteries in supplying the heart muscle with blood.

It is the efficiency of the Thebesian circulation in this rôle, most likely, that explains the few clinical symptoms as well as the absence of heart failure. The same explanation almost certainly accounts for the absence of signs and symptoms of heart failure in those patients with advanced sclerosis which practically occludes both coronary arteries. In many instances these are first discovered by the pathologist.

The interesting point is that both syphilitic aortitis and sclerosis of the coronary arteries are relatively slow processes. The occlusion of the artery is gradual in each instance—so gradual, indeed, that the

Thebesian vessels have time to take over the new duty and readjust themselves to it. The element of time is apparently a very important factor.

Nowhere in the body is the adaptability of the human mechanism better illustrated than in the capacity of the heart, while functioning at full speed, to effect a complete revolution in the cardiac circulation, provided that the need for the change is brought about gradually.

SUMMARY

Two cases of essential closure of both coronary orifices are reported. The lesions indicate a slowly progressive process which has probably taken months at least to reach the point of essentially complete closure. No evidences of fatty change, myocarditis or repair were found in the heart muscle.

The only adequate explanation of the ability of these patients to live and work rests upon a belief that the Thebesian veins have supplied the compensatory circulation necessary for the functioning of the heart muscle.

REFERENCES

1. Klotz: Brit. M. J. 2: 1767, 1906.
2. Gurd and Wade: J. M. Research 20: 85, 1911.
3. Albutt, Sir Clifford: Diseases of the Heart, Including Angina Pectoris, London, The Macmillan Co. 2: 21, 1915.
4. Vaquez: Diseases of the Heart, Philadelphia, 1924, p. 413, W. B. Saunders Co.
5. Cabot, R.: Facts About the Heart, Philadelphia, 1926, p. 520, W. B. Saunders Co.
6. Rondeau: Bull. Soc. Anat., Paris, 1865, 253.
7. Warthin, A. S.: Syphilis of Medium and Smaller Vessels, N. Y. M. J. 115: 69, 1922.
8. Scott: Syphilitic Aortic Insufficiency, Arch. Int. Med. 34: 645, 1924.
9. Clawson and Bell: Arch. Path. and Lab. Med. 4: 922, 1927.
10. Vieussens: Nouvelle decouvertes sur le coeur, Toulouse, 1706.
11. Thebesius: Dissertatio medica de circulo sanguinis in corde, Lugduni Batavorum, 1708.
12. Pratt, F. H.: Am. J. Physiol. 1: 86, 1898.
13. Crainicianu: Virchow's Arch. f. path. Anat. 228: 1, 1922.
14. Wearn, J. T.: J. Exper. Med. 47: 293, 1928.

RECIPROCAL BEATING OF THE HEART; AN ELECTROCARDIOGRAPHIC AND PHARMACOLOGICAL STUDY*

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RECIPROCAL beating of the heart is a disturbance of unusual interest inasmuch as it is one of the few forms of bigeminy in which the mechanism is apparent. The four cases reported in this communication presented certain exceptional characteristics which appear to add to our knowledge of this disorder. In one case the disturbance was sufficiently prolonged to permit extensive pharmacological study.

RÉSUMÉ OF THE LITERATURE

Reciprocal beating of the heart was first described by Mines in 1913.[1] He showed that a single stimulus to an auricle-ventricle preparation from the electric ray or to a ventricle-bulbus preparation from the frog may provoke a continuously circulating excitation wave, the auricular contraction evoking a ventricular response and the ventricular contraction, an auricular response. Although several clinical examples of a disorder of this type were reported, the reciprocal nature of the mechanism was first noted by White in 1915.[2] The electrocardiographic tracings of White's case showed atrio-ventricular rhythm, the ventricle beating first and being followed at an interval by an auricular beat. When the R-P interval widened to a certain critical value, the auricular beat gave rise to a second ventricular response. The phenomena described by Mines and by White differ only in degree, the reciprocal beats of the auricle and ventricle as described by Mines continuing indefinitely, while in the clinical examples reported by White, the mechanism terminated abruptly after the second ventricular response. Since 1915 similar instances have been reported by White,[3] Gallavardin and Gravier,[4] Bishop[5] and Dock.[6] The condition was first termed reciprocal rhythm by Drury[7] who observed this type of disorder in a patient with paroxysmal tachycardia of A-V nodal origin. An instance of reciprocal beating in which the auricular contraction gave rise to a ventricular response, followed in turn by a second auricular response, recently has been reported by Wolferth and McMillan.[8]

CASE I. (C.W.)

The patient was a colored widower, 57 years of age, who entered the hospital May 22, 1928 complaining of shortness of breath. He had contracted

*From the Thorndike Memorial Laboratory of the Boston City Hospital, the Medical Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

syphilis about 20 years previously. Six months before entry he was awakened at night by severe precordial pain which persisted for three days and then suddenly disappeared. Three months before entry he noted the onset of dyspnea and a persistent productive cough. One week before entry swelling of the legs developed.

Physical Examination showed a fairly well developed, moderately orthopneic colored man. The pupils were slightly irregular, and reacted sluggishly to light and accommodation. The veins of the neck were markedly engorged. Numerous moist râles were heard everywhere over both lungs except at the bases where the physical signs of fluid were elicited. The heart was greatly enlarged both downward and to the left. The heart sounds were of poor quality; the rhythm was regular except for an extrasystole every three or four beats. There was a blowing systolic murmur at the apex transmitted to the axilla. The peripheral vessels were markedly sclerosed and tortuous. The blood pressure was 190 mm. Hg. systolic; 112 mm. Hg. diastolic. Signs of free fluid in the abdomen were present. The liver was greatly enlarged. There was marked pitting edema of the legs, thighs and back. The Kahn and Wassermann reactions were positive.

The clinical diagnoses were hypertension, myocardial failure, syphilis, generalized arteriosclerosis, hydrothorax (right) and possible coronary occlusion. The first electrocardiogram was taken after the patient had received full doses of digitalis and showed reciprocal rhythm. All electrocardiograms described below were taken after digitalis had been omitted for eight days.

Cardiac Mechanism.—The control tracings of this patient (Figure 1) show atrio-ventricular rhythm with coupling every third or fourth beat, without evidence of independent auricular activity. The origin of the unusual rhythm is either in the A-V node or in the bundle of His above the bifurcation, for the ventricular complexes are of the supraventricular type. Each ventricular beat gives rise, by retrograde conduction, to an auricular contraction represented in the tracings by diphasic P-waves. In most of the reported cases of A-V rhythm, the retrograde P deflection falls clear of the ventricular deflection and is almost always related in a constant manner, the Q-P interval remaining constant. In this case, however, the relation between the initial ventricular deflections and the consequent auricular deflections is constantly changing owing to retrograde heart-block, the Q-P interval gradually increasing from 0.12 seconds in cycle A to 0.16 seconds in cycle B, and finally to 0.26 seconds in cycle C. In cycle C the Q-P interval is sufficiently great to enable the ventricle to recover from its refractory phase. The auricular wave therefore re-enters and excites another ventricular response, Y. The gradual increase in the Q-P interval signifies an increasing delay in retrograde conduction and is analogous to the gradual increase in the P-R interval seen more frequently in downward conduction in heart-block.

In all the many tracings observed, a premature beat occurred only when the Q-P interval was at least 0.26 seconds. The longest Q-P interval not followed by a premature ventricular response reached a value of 0.20 seconds. The refractory period of the ventricle in this case may therefore be placed within the limits of from 0.20 to 0.26

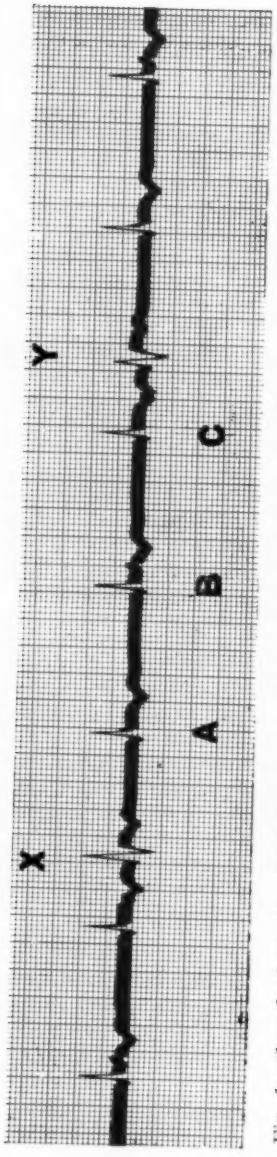

Fig. 1.—Case I. Lead II. Atrio-ventricular rhythm with retrograde heart-block. The retrograde P-waves are followed by a second ventricular response at X and Y.

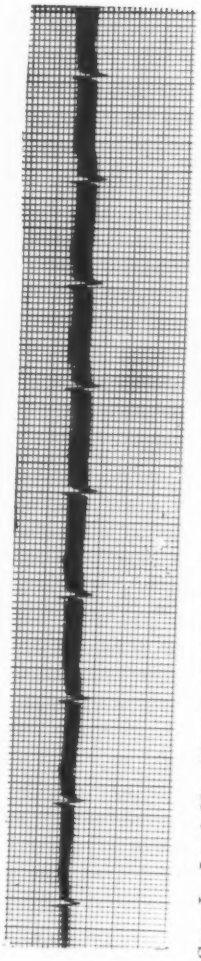

Fig. 2.—Case I. Lead II. Electrocardiographic tracings after 0.002 gm. atropine subcutaneously. Atrio-ventricular rhythm with abolition of reciprocal rhythm. Standardization was difficult because of high resistance.

seconds. The interval from the extra re-entrant beat to the next normal beat was approximately the same as between the usual nodal beats. This time relation is similar to that observed in patients with sino-auricular rhythm and auricular extrasystoles.

It is interesting to note that the Q-P interval was 0.26 seconds, whereas the P-R interval of the reciprocal beat was 0.28 seconds. The degree of block to retrograde conduction in this instance is approximately the same as that to downward conduction. This finding is exceptional, and is in contrast to that observed by White[2] in one case in which the Q-P interval was longer than the P-R interval,—0.378 seconds as compared with 0.24 seconds in one of the digitalis couples, and 0.376 seconds as compared with 0.289 seconds in one of the vagal pressure couples. As in our case, and in the instance of paroxysmal tachycardia of A-V origin reported by Drury,[7] the reciprocal ventricular beat appeared only when the Q-P interval exceeded a certain interval.

The constancy of the electrocardiographic phenomena displayed by the patient afforded an exceptional opportunity to study more intimately the mechanism and so the following observations were made.

THE EFFECT OF EXERCISE

After exercise, the ventricular rate rose from 79 to 94, falling to 82, two minutes after the completion of exercise, and to 76, five minutes after the completion of exercise. Exercise completely abolished the reciprocal beats so that the rhythm became regular. Examination of the tracings indicates that this change was due to the fact that the Q-P interval became shorter and so was not sufficiently great to permit the A-V node to recover from its refractory phase and transmit the re-entrant wave. The tracing was similar to that observed after atropine (Figure 2). The shortening of the Q-P interval was doubtless due to the inhibition of the vagus nerve which occurs on exercise[9] and is analogous to the disappearance of reciprocal rhythm after atropine observed by Bishop.[5] It is significant that in the case of atrio-ventricular rhythm observed by Gallavardin and Gravier,[4] reciprocal rhythm was present only when the vagus nerve was stimulated by pressure. Interruption of reciprocal rhythm by exercise was also observed in a patient studied by White.[3]

THE EFFECT OF VAGAL PRESSURE

In the absence of vagal pressure, reciprocal beats occurred every third or fourth cycle. Either right or left vagal pressure lengthened the Q-P interval so that the Q-P interval of the first returning cycle was 0.12 seconds, of the second cycle, 0.30 seconds. The latter auricular impulse re-entered and excited a second reciprocal ventricular

beat. A reciprocal ventricular beat consequently occurred every second cycle. The increased number of reciprocal beats led to a slight rise in the ventricular rate.

The P-R interval of the reciprocal beat was 0.16 seconds, instead of 0.28 seconds as in the control records. This shortening of P-R was probably due to more complete recovery of the A-V node during the increased Q-P interval. It is of interest that the converse of this situation has likewise been observed, that is to say, with shortening of the Q-P interval and a lessened opportunity for the A-V node to recover, the P-R interval of the re-entrant beat becomes lengthened. This inverse relation between the Q-P and P-R intervals was noted by Sherf and Shookhoff[10] experimentally and is in accord with observations by White.[3]

THE EFFECT OF EPINEPHRIN

The administration of 0.5 c.c. of a 1:1000 solution of epinephrin intramuscularly did not abolish the reciprocal rhythm. The Q-P and P-R intervals were not altered. An additional 0.5 c.c., 12 minutes later, produced no further changes. These observations indicate that the disappearance of reciprocal beats after exercise was not due to stimulation of the sympathetic nerves.

THE EFFECT OF PHYSOSTIGMINE

One milligram of physostigmine was injected subcutaneously, and electrocardiograms were taken at five minute intervals for thirty minutes, after which two additional milligrams were given. It was thought that physostigmine, by stimulating the vagus, might produce more frequent reciprocal beats. No such effect was observed, however.

THE EFFECT OF ATROPINE

The absence of any effect by epinephrin suggested that the disappearance of the reciprocal beats on exercise was due to the inhibition of the vagus.[9] To test this possibility, two milligrams of atropine sulphate were given subcutaneously and electrocardiograms were taken at frequent intervals during the following half hour. Atropine completely abolished the reciprocal rhythm (Figure 2) by shortening the Q-P interval to 0.12 seconds or less. No evidence of independent sino-auricular activity could be seen in any tracing.

This effect of atropine in abolishing reciprocal rhythm was noted by Bishop[5] but was absent in the case reported by Dock.[6] In the case reported by White in 1921,[3] atropine sulphate failed to affect the bigeminal rhythm because the Q-P interval was not sufficiently decreased.

Frequent tracings were taken during the following days of the patient's life. The amplitude of the QRS complex lessened conspicu-

ously and the cardiac rate dropped to 40 per minute with reciprocal beats following each nodal beat. In several tracings questionable extra ventricular systoles were observed.

COMMENT. Reciprocal beating of the heart in this patient seemed to be influenced mainly by vagal hypertonicity for, while epinephrin failed to affect the rhythm, both atropine and exercise completely abolished the reciprocal beats. The more frequent occurrence of reciprocal beats on vagal pressure is in accord with these observations. We are unable to explain the absence of any effect by physostigmine.

Similar to nearly all previously observed cases of reciprocal rhythm, the second ventricular complexes were aberrant in form. This is presumably due to transmission of the impulse downward during the partial refractory phase of the ventricle.

In reciprocal rhythm the retrograde P-waves are excited by the preceding ventricular beats so that, if the ventricular rhythm is regular, the retrograde P-waves will likewise be in a somewhat regular relationship to each other. It may be thought that the tracings of this patient might be otherwise interpreted as an instance of complete auriculo-ventricular dissociation, the auricles beating at a rate of 50 per minute and the P-waves, when they fell in a certain phase of the diastolic period, occasionally giving rise to ventricular beats. The following considerations weigh against the possibility of an independent auricular rhythm. (1) The P-waves were more closely related to the preceding ventricular complexes than to each other. (2) Exercise failed to cause a significant increase in the auricular rate. (3) Vagal pressure did not slow the auricular rate. (4) Atropine was without effect on the auricular rate. (5) The abolition of the bigeminy by atropine and exercise and the increased frequency of the disturbance in rhythm on vagal pressure conform to the previous observations on reciprocal beating of the heart and are inexplicable according to the other interpretation.

CASE II. (F.S.) The patient was a white widower, 55 years of age, who entered the hospital September 8, 1925 complaining of swelling of the legs. His past history was irrelevant. He had felt well until two years before admission when he noted gradually increasing breathlessness on exertion. One year before admission he noticed occasional swelling about the ankles. Four weeks before admission the symptoms became more marked and he was troubled by a productive cough. Four days before admission he was forced to discontinue work.

On *physical examination* the antero-posterior diameter of the chest appeared considerably increased. The percussion note was everywhere hyperresonant. There was a moderate number of medium moist râles at both bases. Expiration was prolonged. The cardiac borders could not be percussed out because of the hyperresonance of the chest. The heart sounds were distant, and coupled rhythm could be heard. No murmurs were audible. The peripheral vessels were moderately thickened and tortuous. The blood pressure was 130 mm. of mercury, systolic; 80 mm. diastolic. The tender edge of the liver was palpable 4 cm. below the costal

margin. There was conspicuous pitting edema of the legs and genitalia. The reflexes were normal. The Wassermann reaction of the blood was negative. The electrocardiograms described below were taken after the patient had been fully digitalized. The patient's condition gradually improved, and he was able to leave the hospital October 12, 1925.

The diagnoses were *generalized arteriosclerosis, myocardial failure and pulmonary emphysema.*

Cardiac Mechanism.—The electrocardiographic tracings of this patient show atrio-ventricular rhythm with right bundle-branch block (Fig. 3). As in Case I, reciprocal rhythm is clearly present. In the first three pairs of Lead I (Figure 3), the Q-P intervals are approximately 0.36 seconds, while the P-R intervals of the reciprocal beats are approximately 0.32 seconds. Downward conduction is evidently easier than upward or retrograde conduction, a relation similarly observed in the case reported by White.[2] This also has been observed experimentally, the Vs-As of retrograde beats being longer than the As-Vs interval in the same animal.[10] The seventh cycle in Figure 3 is not followed by a re-entrant beat. Here the Q-P interval of 0.32 seconds evidently was insufficient to permit recovery of the A-V node. In Lead II (Figure 4) the R-P interval of the second ventricular complex is 0.36 seconds with a P-R interval of the reciprocal beat of 0.26 seconds. This relation is also present in the fourth and fifth cycles. The sixth ventricular complex is followed by a retrograde P-wave after an interval of 0.32 seconds, an interval which evidently was insufficient to enable the ventricle to recover from its refractory phase. In no place is there evidence of independent auricular activity, the P-waves always succeeding the ventricular deflection and in some instances being followed by a second ventricular complex.

CASE III. (D.J.T.) The patient was 55 years of age, and entered the hospital June 16, 1915. Nine months prior to admission he first experienced sharp, agonizing pain over the heart. The attacks of pain occurred at night and lasted four to five hours. Six weeks before entry to the hospital, breathlessness occurred on exertion. Ten days before admission edema of the legs developed.

Physical examination showed extreme dyspnea, orthopnea and cyanosis. Respiration was periodic. The peripheral vessels were tortuous and sclerosed. Medium and coarse moist râles were heard everywhere over both lung areas. The cardiac impulse was diffuse but not forcible and was maximal in the sixth interspace, 17 cm. to the left of the midsternal line. The sounds were of fair quality. The second aortic sound was louder than the second pulmonic sound and was somewhat accentuated. A definite protodiastolic gallop rhythm and occasional extrasystoles were heard. No murmurs were audible. The liver was moderately enlarged and slight edema of the feet and ankles was present. The blood pressure was 184 mm. of mercury, systolic, and 140 mm. diastolic. Electrocardiographic tracings on June 17 showed normal sinus rhythm. The tracings described below were taken after the patient had received 0.1 gram of digitalis leaves three times daily for 4 days. After rest in bed the patient improved and left the hospital, July 18, 1915. He died at home on February 17, 1916.

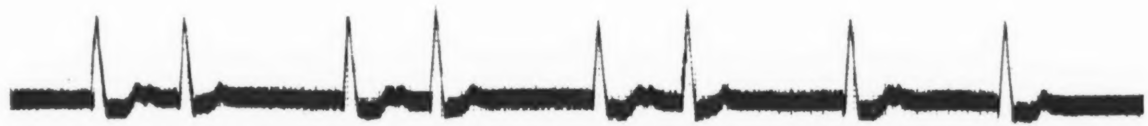

Fig. 3.—Case II. Lead I. Reciprocal rhythm is present in the first three pairs of beats with Q-P intervals of approximately 0.36 second, and P-R intervals of the reciprocal beats of approximately 0.32 second.

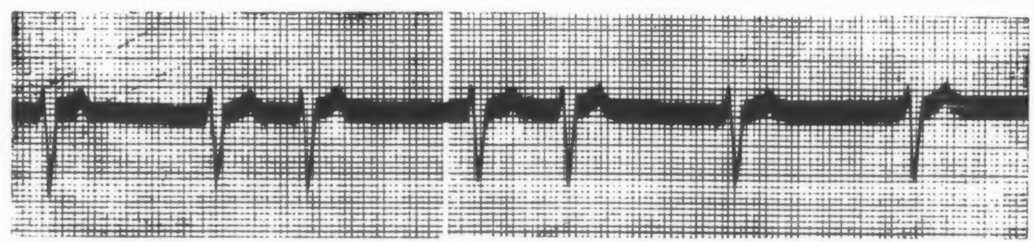

Fig. 4.—Case II. Lead II. Showing essentially the same features as the tracings of Fig. 3.

Cardiac Mechanism.—The tracings (Figures 5, and 6) in this case show reciprocal beating of the heart, with A-V nodal rhythm and retrograde heart-block. In Lead I, (Fig. 5) the R-P interval of cycle A is 0.12 seconds, of cycle B, 0.18 seconds and of cycle C, 0.40 seconds, the latter P-wave being followed by a ventricular response. In this lead, lead II (Figure 6), and lead III, the P-R interval of the reciprocal beats is much shorter than the immediately preceding Q-P interval. This is in contrast to the observation in Case I but is similar to the findings in Case II and in one of White's patients.[2]

CASE IV. (H.L.H.) The patient was 44 years of age, and entered the hospital, May 22, 1926 complaining of shortness of breath. Two years before admission he noticed dyspnea on exertion, and three weeks before admission swelling of the legs and distention of the abdomen appeared. *Physical examination* showed orthopnea and marked cyanosis, congestion of the lungs and free fluid in the chest and abdomen. The heart was greatly enlarged. The heart sounds were of poor quality and coupled rhythm was present. At the base the second aortic sound was absent and there was a loud rough systolic murmur transmitted upwards. A systolic thrill was palpable in the second right interspace. The peripheral vessels were moderately sclerosed and tortuous. The blood pressure was 113 mm. of mercury, systolic and 68 mm. diastolic. There was marked edema of the scrotum, thighs and legs. Examination of the blood including the Wassermann reaction showed no abnormalities.

The clinical diagnoses were *cardiac decompensation, aortic stenosis, chronic myocarditis, general anasarca.* The electrocardiographic tracings were taken before digitalis could have taken effect. The patient became rapidly worse and died within a few hours after admission to the hospital.

Post-mortem examination showed *chronic endocarditis, aortic stenosis, hypertrophy and dilatation of the heart, anasarca, bronchopneumonia and chronic passive congestion of the viscera.*

Cardiac Mechanism.—The tracings of this patient (Figure 7, Figure 8) show the most marked variations in retrograde block of any hitherto observed. These variations confirm in certain details the observations on the preceding three cases. The ventricular deflection of cycle A, in Figure 7, is preceded by an inverted P-wave. The ventricular deflection is of supraventricular origin. The occurrence of the P-wave before the ventricular deflection is evidently due to facilitation of the spread of the excitation wave upwards so that the auricular response occurs at an appreciable interval before spread of the excitation wave downwards over the ventricle (approximately 0.12 seconds in this instance). In cycle B passage of the excitation wave evidently encounters more difficulty, for the P-wave seems to be buried in the QRS deflection. In cycle C the P-wave follows the initial portions of the QRS deflections by approximately 0.12 seconds. The retrograde P-wave distorts the S-T interval and causes more marked inversion of the T-wave. In cycle D the R-P interval has increased to 0.28 seconds. The ventricle has evidently recovered from the absolute refractory stage for a ventricular response immediately follows the P-wave (cycle E). The aberrant form of this complex probably is due to the

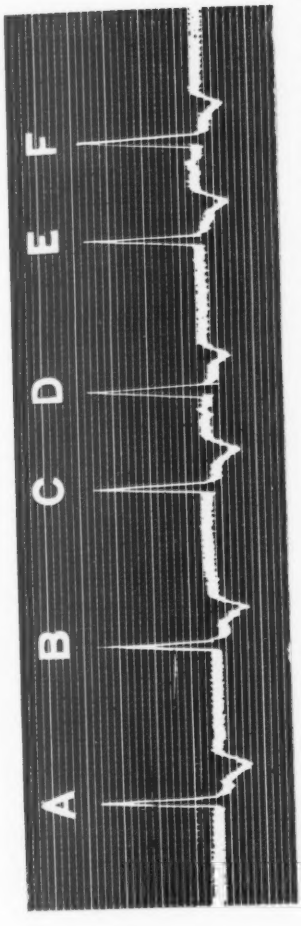

Fig. 5.—Case III. Lead I. Atrio-ventricular rhythm, partial retrograde heart-block and reciprocal beats at D and F.

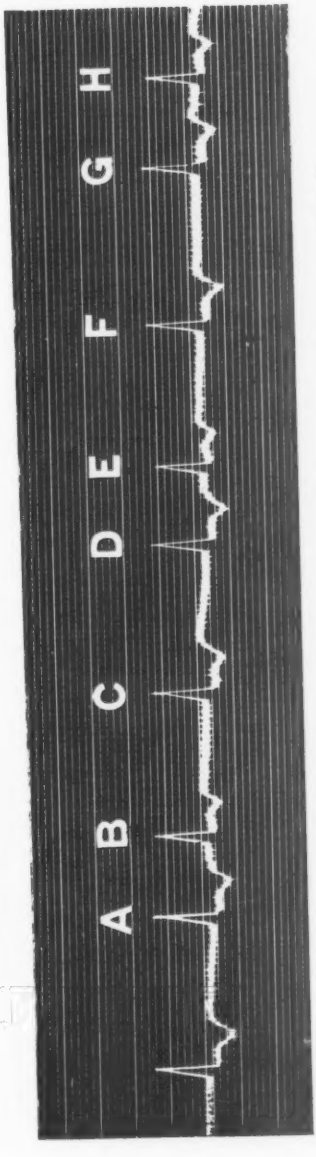

Fig. 6.—Case III. Lead II. Showing essentially the same features as Fig. 5.

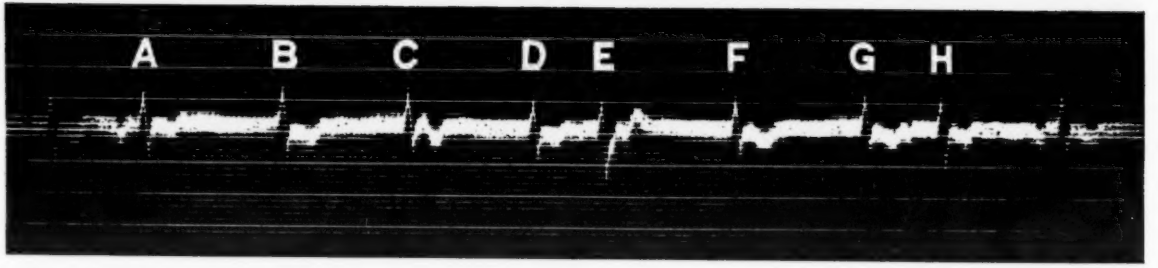

Fig 7.—Case IV. Lead II. In cycle A the inverted retrograde P-wave precedes the ventricular deflection. In succeeding cycles the P deflections appear progressively later in relation to the ventricular complex due to partial retrograde heart-block. Thus in cycle B the P-wave is evidently buried in the QRS deflection while in cycle C, it deforms the S-T interval. Finally in cycle D, the R-P interval is widened to such an extent that the P-wave falls sufficiently clear of the refractory phase of the ventricle to excite another ventricular response, cycle E. The aberrant form of the ventricular deflection of cycle E is evidently due to the fact that the ventricle is still in the partially refractory phase.

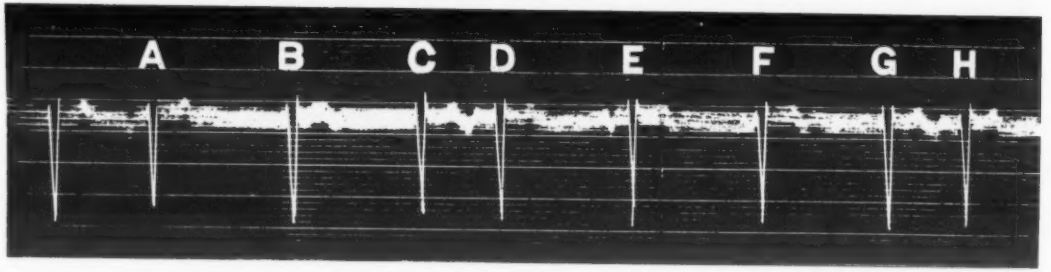

Fig. 8.—Case 4. Lead III. In cycle A, the sharply inverted retrograde P-wave precedes the ventricular deflection. In cycle B, the P-wave causes notching of the T-wave while in cycle C, it falls on the terminal portion of T and excites a second ventricular response. This chain of events is repeated in the remaining cycles of this tracing.

fact that the response occurred while the ventricle was still in the partial refractory phase. This interpretation is supported by cycles G and H. The R-P interval in cycle G is 0.04 seconds longer than in cycle D; the ventricle has had a longer period of time in which to recover and consequently the succeeding reciprocal cycle H beat is more nearly normal in outline.

Similar events are shown in Figure 8 which is a tracing from Lead III. In the first cycle following the previous reciprocal beat, the P-wave appears before the ventricular deflections. In cycle B, the P-wave depresses the S-T interval and causes notching of T. In cycle C the R-P interval is approximately 0.32 seconds, and a reciprocal beat of the heart follows. The degree of retrograde block shown in this case is not uniform so that reciprocal beats occur every third, fourth, or fifth cycle. As might have been expected with such varying R-P intervals, the P-R intervals likewise vary, the shorter R-P intervals being followed by longer P-R intervals of the reciprocal beats. The characteristic pairs of ventricular complexes with an inverted auricular deflection sandwiched between are seen in cycles C and D, and G and H.

SUMMARY

The clinical and electrocardiographic aspects of four cases of reciprocal beating of the heart are recorded and the nature of the abnormal mechanism is discussed.

In one case the disturbance was sufficiently prolonged to permit extensive pharmacological study. This study indicated that reciprocal beating was influenced mainly by vagal hypertonicity.

It is a pleasure to acknowledge our indebtedness to Dr. Henry A. Christian for the use of the records of the Peter Bent Brigham Hospital and to Dr. Samuel A. Levine for his helpful suggestions.

REFERENCES

1. Mines, G. R.: Dynamic Equilibrium in the Heart. Reciprocating Rhythm. J. Physiol. **46**: 376, 1913.
2. White, P. D.: A Study of Atrio-ventricular Rhythm Following Auricular Flutter. Arch. Int. Med. **16**: 517, 1915.
3. White, P. D.: The Bigeminal Pulse in Atrio-ventricular Rhythm. Arch. Int. Med. **28**: 213, 1921.
4. Gallavardin, L. and Gravier, L.: Bradycardie Nodale, Permanente Étude du Rhythme Atrio-ventriculaire. Arch. d. mal. du Coeur. **14**: 71, 1921.
5. Bishop, L. F.: Specific Action of Atropine in Relieving Certain Irregularities of the Heart Beat. J. A. M. A. **67**: 31, 1921.
6. Dock, W.: The Reciprocal Rhythm. Arch. Int. Med. **41**: 745, 1928.
7. Drury, A. N.: Paroxysmal Tachycardia of A-V Nodal Origin, Exhibiting Retrograde Heart-Block and Reciprocal Rhythm. Heart. **12**: 405, 1924.

8. Wolferth, C. C. and McMillan, T. M.: Observations on the Mechanism of Relatively Short Intervals in Ventriculo-auricular and Auriculo-ventricular Sequential Beats During High Grade Heart-Block. Am. Heart J. **4**: 521, 1929.

9. Hunt, R.: Direct and Reflex Acceleration of the Mammalian Heart, with Some Observations on the Relations of the Inhibitory and Accelerator Nerves. Amer. J. Physiol. **2**: 436, 1899.

10. Sherf, D. and Shookoff, C.: Experimentelle Untersuchungen über die Umkehr Extrasystole. Wien. Arch. f. inn. Med. **12**: 500, 1926.

THE MECHANISM OF TRANSITIONS FROM AURICULO-VENTRICULAR DISSOCIATION TO S-A RHYTHM; ITS RELATION TO THE THEORY OF PARASYSTOLE*

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BIGEMINAL rhythm has been the subject of considerable study, not only because it is intrinsically important, but also because knowledge of its mechanism may aid in understanding other cardiac irregularities such as paroxysmal tachycardia. At the present time there are two prevailing theories concerning the mechanism of coupled beats, the theory of re-entry and the theory of parasytole. According to the former theory, the second extra beat is excited by the re-entrant wave of the preceding normal systole. According to the theory of parasystole, the extra beat is not related to the normal systole, but is one of a series of impulses built up slowly and rhythmically by another independent center. The two impulse centers, the one normal, the other arising anew, are in the main independent but may not be completely so, for premature beats may be liberated from one center by the occasional receipt of an impulse from the other.

In a previous communication[1] four examples of coupled rhythm were reported in which the mechanism seemed explicable according to the theory of re-entry. The tracings showed atrio-ventricular rhythm with occasional coupled beats. An inverted or diphasic auricular complex was sandwiched between the two coupled beats. The mechanism of the disturbance was interpreted as follows. The impulses originated in the A-V node with propagation of the impulse upward over the auricles and downward into the ventricles. In succeeding cycles, ventricle-to-auricle conduction became more and more difficult because of retrograde partial heart-block, the auricular complex occurring progressively later in relation to the ventricular deflection until the Q-P interval was sufficiently great to allow recovery of the ventricle from its refractory phase. When the Q-P interval reached a certain critical value, the P-wave evidently re-entered the ventricle and excited a second ventricular response. The coupling displayed by the four cases was explicable, therefore, according to the theory of re-entry.

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The following two cases are examples of coupling, the mechanism of which seems clearly in accord with the other theory, the theory of parasystole.

CASE I.

M.E.Y., was a colored widow of 47 years who had been in the hospital from May 19, 1925 to July 30, 1925. At that time she had complained of a productive cough and breathlessness of one month's duration. Physical examination showed essentially the same abnormalities as on the present admission except for scattered areas of consolidation in both lungs. The clinical diagnoses were bronchopneumonia, circulatory insufficiency and syphilis. With rest in bed and digitalis, she improved and felt fairly well for 4 months or until five months before the present entry when she noted the gradual onset of abdominal enlargement, breathlessness and palpitation of the heart. Because of these symptoms she was forced to enter the hospital again on April 28, 1926.

Physical examination showed a very dyspneic negress with slight edema of the face. The pupils were irregular and did not react to light. The heart was slightly enlarged to percussion. The underlying cardiac rhythm was regular, but was interrupted by an occasional extrasystole. There was a soft systolic murmur at the apex. The blood pressure was 230 mm. of mercury, systolic, and 115 mm. diastolic. The radial pulses were equal, synchronous and regular. Both lungs showed the physical signs of congestion and there was fluid at the bases of both lungs and in the abdomen. There was marked pitting edema over the tibiae and ankles. The Wassermann reaction was positive. The urine showed a trace of albumin with many waxy casts. The electrocardiographic tracings shown below (Figures 1 & 2) were taken May 17, 1926. During the preceding week the patient had taken a total of 1 gram of digitalis leaves. In spite of treatment, she grew progressively worse and died on June 21, 1926.

An autopsy was performed. The heart weighed 380 gms. On section the myocardium was found to be thickened and a moderate number of fibroid patches was present. The heart valves were normal. Numerous linear scars of the aorta were apparent just above the aortic valve and the intima was drawn into folds. The pathological diagnoses were chronic nephritis, tuberculosis of the left kidney, hypertrophy and dilatation of the heart, edema and atelectasis of lungs, chronic polyserositis, cirrhosis of liver, pyosalpinx, endometritis, syphilis and generalized arteriosclerosis.

Cardiac Mechanism.—The first four cycles of Figure 1 show normal sino-auricular rhythm, with P-R intervals of 0.15 seconds. The inter-auricular intervals between P_1, P_2, P_3, and P_4 are 0.70 second, 0.70 second and 0.71 second. The next auricular impulse, P_5, appears after 0.76 second. Before the impulse can be transmitted to the ventricle, the latter manifests its own inherent rhythm by escaping from sino-auricular control. P_5, P_6, P_7, and R_5, R_6, R_7, R_8 are unrelated, the electrocardiographic tracing showing complete auriculo-ventricular dissociation. Since the ventricular rate is faster than the auricular during this period of dissociation, the auricular deflections fall progressively later in relation to those of the ventricle. Hence, P_5 precedes R_5, while the diminution of S and the slightly increased height of R_6 indicate that P_6 is buried in the ventricular deflections. P_7 is

represented by the peaked S-T interval in R_7, while in R_8 the inversion of T is almost obliterated by the simultaneous occurrence of P_8. P_8 occurs 0.23 second following the onset of the preceding ventricular deflection, R_8, an interval sufficiently great to permit the ventricle to recover from its refractory phase. The auricular beat, P_8, consequently excites a premature ventricular response, R_9. The P-R interval of this coupled beat is 0.25 second, an interval somewhat greater than that during normal sinus rhythm. This increase in conduction time is probably due to transmission of the P-wave during the partial refractory phase of the A-V node.

The relatively prolonged P-R interval of P_8-R_9 allows the auricle to send another impulse, P_9, across the A-V node before the ventricle can build up its next impulse. P_9 consequently forces a ventricular response, R_{10}, after an R-R interval of only 0.66 second. The sequence of events then repeats itself, P_{10} stimulating a ventricular deflection R_{11}, while with R_{12} escape of the ventricle again becomes evident. The inherent rhythmicity of the ventricles in this tracing is higher than that of the auricles and so it may seem curious that the A-V node did not assume complete control of the auricles and ventricles. The failure of the A-V node to assume control is due to the blocking of all retrograde impulses from ventricle to auricle. The phenomenon of unidirectional block has been noted by other observers both clinically and experimentally and forms one of the important concepts about which the theory of parasystole is built. A similar form of coupling occurring in almost complete auriculo-ventricular dissociation has been observed, in a very few instances, by Hewlett,[2] White,[3] and Mobitz,[4] but so far as we are aware, no examples occurring with repeated transitions from S-A rhythm to complete auriculo-ventricular dissociation have previously been reported.

The case studied by Hewlett[2] showed complete dissociation except rarely when the auricular impulse descended upon the ventricle after a certain critical interval, and excited a premature beat of the ventricle. The P-R interval of the premature beats varied from 0.48 to 0.60 second. Auriculo-ventricular sequence was absent except for these rare beats. Reverse conduction from the ventricles to the auricle was so depressed that no retrograde P-waves were present. The case reported by White[3] was similar, complete dissociation being present except for rare beats showing A_8-V_8 sequence. The P-R interval of the premature beats with transient auriculo-ventricular association was approximately 0.30 second. In all cases reported, the ventricular rate was higher than that of the auricles and reversed conduction from ventricles to auricles was absent.

Figure 2 is an electrocardiographic tracing, Lead III, from Case I. The mechanism of the irregularity is essentially the same as that shown in Lead I (Fig. 1). The tracing (Fig. 2) offers certain data

which corroborate the interpretation of the mechanism of the electrocardiogram of Lead I. P_1 is followed after an interval of 0.16 second by a normal ventricular response. Although P_2 precedes R_2 by 0.12 second, the ventricular deflection is of an aberrant type indicating that ventricular escape has occurred. P_2, P_3, P_4, P_5 and R_2, R_3, R_4, R_5, and R_6 show complete auriculo-ventricular dissociation. The ventricular rate is faster than the auricular so that the P-waves fall progressively later in relation to the ventricular complexes. During the period of complete dissociation the auricular impulses reach the ventricle while it is evidently still in the refractory phase. P_6 falls late enough, however, to incite a ventricular response, R_7. The contours of R_7 and R_8 indicate responses of the supraventricular type. Beginning with P_8 and R_9 complete dissociation is again evident. The previously described events then repeat themselves, P_{11} finally evoking a ventricular response, R_{13}, after a P-R interval of 0.28 second. Of the two P-waves, P_6 and P_{11}, which excite premature beats in this tracing, P_{11} occurs 0.07 second closer to the onset of the preceding ventricular deflection than P_6. The R-P interval of R_6-P_6 is 0.25 second, while the R-P interval of R_{12}-P_{11} is 0.18 seconds. The longer P-R interval of P_{11}-R_{13} is consequently to be explained by the P-wave reaching the ventricle earlier when the latter is more refractory. In Lead I the R_8-P_8 interval was 0.23 second and the P_8-R_9 interval 0.25 second, intervals closely similar to those of R_6-P_6 and P_6-R_7 in Lead III.

The tendency of the arrhythmia to repeat itself, to which the term *allorhythmia* has been applied, is of considerable interest. Kaufmann and Rothberger[5] observed that if the regularly beating auricle or ventricle of the dog or cat is exposed to a series of rhythmic shocks at any rate lower than the natural beat, a simple allorhythmia appears. This allorhythmia consists of premature beats occurring at certain regular intervals. It is the result of the regular interference with the building up of natural impulses by stimuli emanating from another independent source. The effective shock breaks down the stimulus material at the natural pacemaker prematurely and is followed by a pause of fixed length. As in Case I, the time relations between any two such rhythms leads to regular repetition of premature responses as soon as the time relation between the beat of one rhythm and the beat of the other rhythm reaches a certain critical value.[6]

The tracings of Figures 1 and 2 are clinical examples closely analogous to the phenomena observed by Kaufmann and Rothberger. The auricular impulses in these tracings are comparable to the series of rhythmic shocks to which the regularly beating ventricle is exposed. The time intervals of these clinical tracings are not as precise as those found experimentally, due probably to the influence of the extra cardiac nerves.

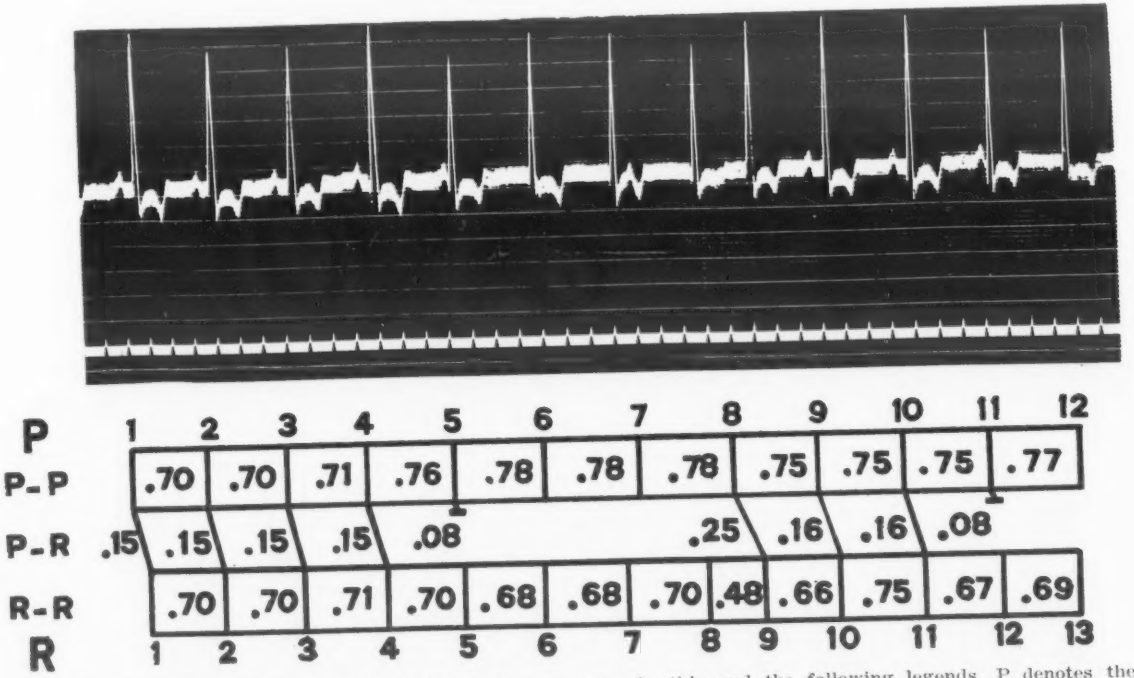

Fig. 1.—Lead I. Time is indicated in fifths of a second. In this and the following legends, P denotes the P-waves; P-P, the interauricular intervals; P-R, the interval between the beginning of the "P" and the "R" deflections; R-R, the inter-ventricular intervals; and R, the ventricular complexes. The first four cycles show normal sino-auricular rhythm. P_5, P_6, P_7, and R_5, R_6, R_7 show complete auriculo-ventricular dissociation. P_8 excites a premature ventricular response, R_8. Although there is no evidence of retrograde conduction, the premature response, R_8, is followed by quickening of the auricular rate which enables the sinus node to regain control.

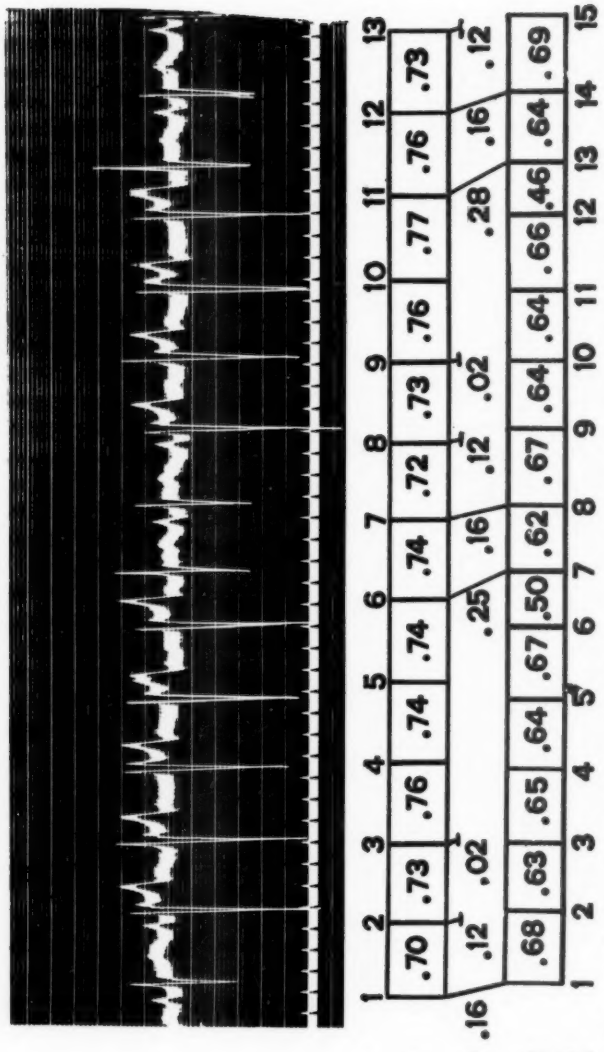

Fig. 2.—Lead III showing three transitions from sino-auricular rhythm to complete auriculo-ventricular dissociation. The relatively slow rate of the auricles prevents the occurrence of more than two successive auriculo-ventricular beats.

CASE II.

T.J.M., a white blacksmith's helper of 22 years, entered the hospital June 30, 1920. He felt well, until 10 days before admission, when he was forced to go to bed because of weakness, fatigue, and the onset of severe, dull substernal pain. There was no palpitation of the heart or swelling of the legs. Because of persistent pain and increasing weakness he decided to enter the hospital.

Physical examination showed orthopnea and marked venous pulsations in the neck. The heart was moderately enlarged downward and to the left. A rough systolic murmur transmitted into the great vessels of the neck and a soft blowing diastolic aortic murmur were heard over the conventional aortic area. The cardiac rhythm was regular except for a premature beat every 8 to 12 cycles. Both first and second sounds of the premature beat were audible. The radial pulses were equal, water hammer in type, and the rate was 60 per minute. The vessel walls were easily compressible. Duroziez's sign and a pistol-shot sound were heard over the femoral artery. The blood pressure was 190 mm. mercury, systolic and 0 mm. mercury diastolic. The lungs were clear and resonant throughout. The vital capacity of the lungs was 4000 c.c. Examinations of the urine and blood were repeatedly negative.

The diagnoses were chronic rheumatic valvular disease, mitral stenosis and insufficiency, aortic insufficiency and stenosis.

The patient responded readily to treatment, and rest in bed. He did not receive digitalis. The electrocardiographic tracings were taken on June 30, 1920. He was discharged July 10, 1920.

He was readmitted August 7, 1921. Physical examination showed essentially the same findings as previously with the exception of the signs of fluid at the bases of the lungs and marked pitting edema of both legs. The electrocardiographic tracings on this admission showed normal sinus rhythm. He died at home, October 13, 1921.

Cardiac Mechanism.—The cardiac mechanism in Figure 3 is similar to that present in Case I. P_1 excites a ventricular response, the transmission interval of 0.21 second, indicating delay in conduction. The inherent rhythmicity of the ventricles is greater than that of the auricles and leads to ventricular escape. P_2, P_3, P_4 and R_2, R_3, R_4 and R_5 show complete auriculo-ventricular dissociation. The relation between the auricular and ventricular beats is such that the auricular impulse occurs progressively later in relation to the ventricular impulses. The auricular impulses are not followed by ventricular responses because they descend upon the ventricles while the latter are evidently refractory. The onset of P_3, for example, precedes the onset of R_3 by 0.08 second, while the onset of P_4 occurs 0.13 second after the onset of R_4. The beginning of P_5 follows the initial deflections of R_5 by 0.22 second, an interval of time sufficiently great to permit ventricular response after a transmission interval of 0.44 second. This increase in the P-R interval of P_5-R_6 indicates partial refractoriness of the A-V node. The forced beat evidently destroys the immature impulse forming in the ventricle and a new impulse is then built up at the usual rate. Following the ventricular response, R_6, the next ventricular beat might have been expected after an interval of approximately 1.13 seconds. But before the ventricle can build up

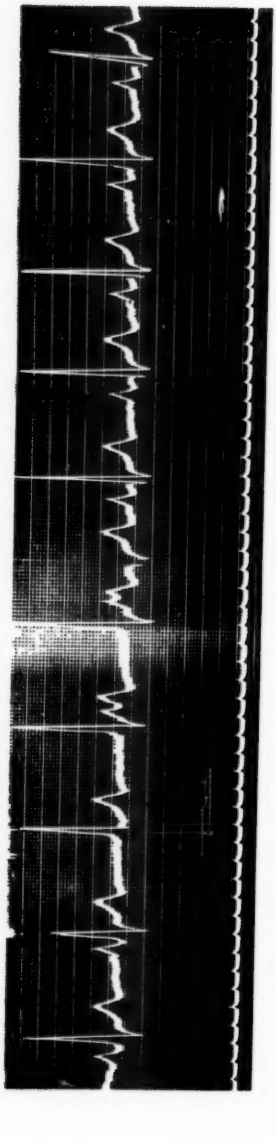

Fig. 3.—Lead II. P_1 excites a ventricular response but P_2, P_3, P_4, and R_2, R_3, R_4, R_5 show complete auriculoventricular dissociation. P_5 excites a ventricular response, R_6, and is followed by a quickening of the auricular rate enabling the S-A node to maintain control of the heart during immediately succeeding cycles.

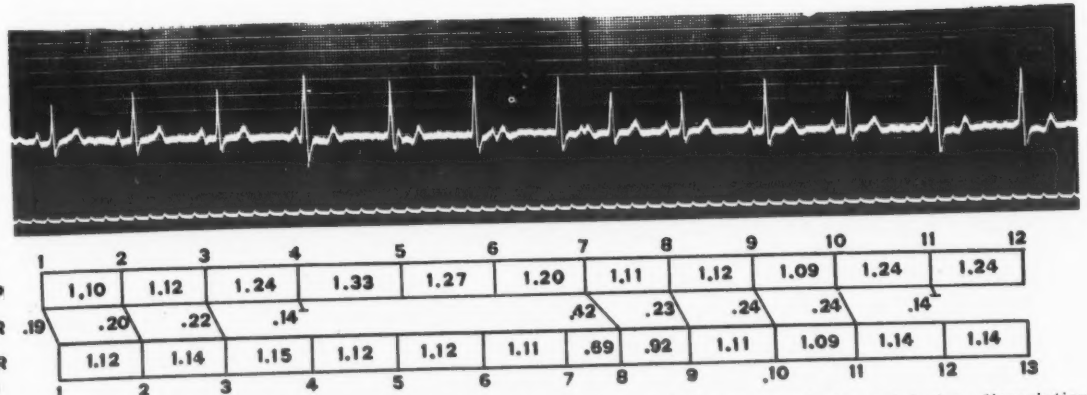

FIG. 4.—Lead III. Case II. Two transitions from S-A rhythm to complete auriculo-ventricular dissociation are present. The premature ventricular beat, R_5, excited by P_7, is coincident with a quickening of the auricular rate.

this impulse, the transmission of P_6, after an interval of only 0.88 second, forces a response R_7. The coupled beat, R_6, is coincident with a quickening of the auricular rate so that the latter approaches the rate of the ventricles. As in Case I, this faster auricular rate enables the S-A node to maintain control of the heart during immediately succeeding cycles. This effect of the ventricular contractions on the rate of the auricular contractions is somewhat surprising in view of the complete block to reversed conduction which was present during the period of complete auriculo-ventricular dissociation. This effect of the ventricle on the auricular rhythm has been noted in clinical examples of complete heart-block by Wilson and Robinson.[7] They observed that the interauricular interval period during which the ventricular systole fell was shorter than those which followed.

Figure 4 shows a tracing of Lead III of Case II. The first three P-waves, P_1, P_2 and P_3 incite normal QRS deflections. P_4, however, precedes R_4 by too short an interval to be responsible for the ventricular response. The aberrant form of the QRS deflections of R_4 is further evidence that escape of the ventricle has occurred. P_4, P_5 and P_6 represent auricular contractions which are entirely dissociated from ventricular deflections, R_4, R_5, R_6 and R_7. P_7, however, falls sufficiently clear of R_7 to excite a ventricular response, R_8, after a transmission interval of 0.42 second. The appearance of the premature coupled beat is coincident with a quickening of the auricular rate so that the S-A node regains and maintains control of the heart until P_{11}. The interauricular interval P_{10}-P_{11} is lengthened and complete dissociation again appears with P_{11}, P_{12} and R_{12}, R_{13}. The tracings of Case II show the same fundamental features as those of Case I. Both show inherent rhythmicity of the ventricles greater than that of the auricles; both show the phenomenon of unidirectional block. The etiology of the heart disease in Case I was syphilitic, in Case II, rheumatic. Both patients showed elevated systolic blood pressures. The abnormal mechanism occurred in Case I after moderate doses of digitalis while in Case II the phenomenon appeared without digitalis.

SUMMARY

1. Electrocardiographic tracings of two patients showing a rare form of bigeminy are described. Although a similar form of coupled rhythm occurring in almost complete auriculo-ventricular dissociation has been observed rarely, no instances occurring in repeated transitions from complete auriculo-ventricular dissociation to S-A rhythm have previously been reported.

2. The period of auriculo-ventricular dissociation was terminated by an A_s-V_s sequence when the auricular impulse descended to the ventricle after an interval of at least 0.46 second in Case I and of at least 0.68 second in Case II. Although reversed conduction from ven-

tricle to auricle was at all times absent, the premature ventricular response was invariably followed by quickening of the auricular rhythm, the S-A node gaining control of the heart for several beats. With subsequent slowing of the auricular rate, complete auriculo-ventricular dissociation again occurred and the cycle of events was repeated.

3. The abnormal mechanism occurred in one case after moderate doses of digitalis; in the other case, in the absence of digitalis medication.

4. The relation of the mechanism to the theory of parasystole is discussed.

We gratefully acknowledge our indebtedness to Dr. Henry A. Christian for the use of the records of the Peter Bent Brigham Hospital and to Dr. Samuel A. Levine for his helpful suggestions.

REFERENCES

1. Blumgart, H. L. and Gargill, S. L.: Reciprocal Beating of the Heart,—An Electrocardiographic and Pharmacological Study. Am. Heart J., **5**: 424, 1930.
2. Hewlett, A. W.: A Case Showing Rapid Ventricular Rhythm with Periods of Auriculo-ventricular Dissociation. Heart, **10**, 9, 1923.
3. White, P. D.: Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater than that of the Auricles. Arch. Int. Med., **18**, 244, 1916.
4. Mobitz, W.: Zur Frage der atrioventrikularen Automie. Deutsch. Arch. f. klin. Med., **141**, 257, 1923.
5. Kaufmann, R. and Rothberger, C. J.: Beitrag zur Kenntnis der enstehungsweise extrasystolischer Allorhythmia. Zeitschr. f. d. ges. exper. Med., **5**, 349, 1917.
6. Kaufmann, R. and Rothberger, C. J.: Beiträge zur enstehungsweise extrasystolischer Allorhythmien. V. Mitteilung. Ueber einfache zahlenmässige Beziehungen zwischen Normal und Extrareizrhythmus bei atrioventrikulären und ventrikulären Extrasystolen. Zeitschr. f. d. ges. exper. Med., **29**, 1, 1922.
7. Wilson, F. N. and Robinson, G. C.: Heart-block. I. Two Cases of Complete Heart-block Showing Unusual Features. Arch. Int. Med., **21**, 166, 1918.

THE QUANTITATIVE ASPECTS AND DYNAMICS OF THE CIRCULATORY MECHANISM IN ARTERIAL HYPERTENSION*

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THE etiological causes of arterial hypertension are manifold. In that sense, arterial hypertension is not a disease entity. Its presence over a prolonged period of time, nevertheless, exerts such an important effect on the entire vascular system and on the functions of a number of organs in man, that it should not be considered so much a symptomatic manifestation as an important morbid state of the body. A number of studies are available in the literature on morphological changes in patients suffering from high arterial blood pressure of long duration. These studies fail to reveal either the etiology or the mechanism of the circulation in the presence of high arterial blood pressure. There is, moreover, a lack of quantitative evaluation of the cardiac work and of the peripheral circulation. The largest part of the available and conflicting information has been obtained from animals with experimentally induced high blood pressure,[1, 2, 3] or from observations of certain qualitative aspects of the circulation in man.[4]

THE PROBLEM

This investigation was undertaken with the hope of shedding light upon the state of the circulation in man in the presence of high blood pressure. Such knowledge may be of aid in the understanding of certain clinical manifestations of this condition and of its complications. A better knowledge of the physiology of hypertension may be of value also in revealing the etiological mechanisms of the disease and thus pave the way for sound therapy.

Reliable methods for the measurement of the dynamics of the circulation in man have not been available until recently. The results of the few investigations that have dealt with the functional aspects of the circulation are in conflict, partly because of the frequent unreliability of the methods used, and partly because of a lack of precise correlation between the clinical state of the patients and the observations made. Throughout the developmental stages of arterial hypertension, just as in other morbid states, continuous changes occur in the bodily functions.

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Without the clinical definition of the condition of the patient the laboratory observations lose their significance.

In the presence of persistent hypertension it is important to obtain knowledge of the functional state of the heart and of the peripheral circulation. Methods for the direct measurement of the work and energy consumption of the heart in man do not exist. An estimation of the efficiency and accomplishment of the heart is, nevertheless, possible through a measurement of the peripheral circulation provided that the function of the cardiac valves is normal. In the evaluation of the state of the peripheral circulation in hypertension the following factors are of primary significance: (1) the pressure gradients in the vascular circuit, (2) the cardiac output per unit of time and per beat, (3) the circulating blood volume, (4) the velocity of blood flow, (5) the viscosity of the blood, (6) the hemoglobin content of the blood, (7) the peripheral resistance of the vascular bed, (8) the relative distribution of blood between the lesser and greater circulation.

If the cardiovascular system is considered as a simple hydraulic system, then an abnormal increase in the circulating blood volume, in the cardiac output, in the peripheral resistance, or in the viscosity of blood would produce hypertension. In reality, however, a number of regulatory mechanisms are active in the body which prevent the development of hypertension under certain conditions. These regulatory functions may influence the circulation independently or in combination with each other. Because of the presence of these regulatory mechanisms, one can not foretell, on the basis of theoretical consideration, the state of the circulation in man. Similarly, the effect of one or two measured aspects of the circulation on a third undetermined factor can not always be predicted. Thus normal and pathological conditions of the cardiovascular system may exist with normal blood pressure, although the blood volume is increased, as occurs following increased fluid intake, in certain types of circulatory failure and in diabetes insipidus. In like manner, the cardiac output and the velocity of blood flow may increase considerably without elevation in the arterial pressure as, for example, takes place with muscular work, in the presence of anemia, and in hyperthyroidism. An increase in the peripheral resistance does not always predicate high blood pressure. This state of affairs may be observed in heart failure and in the presence of vascular spasm. Increased viscosity of the blood is often present with normal blood pressure as occurs in diabetes mellitus, shock, and polycythemia. In these conditions compensatory changes of regulatory functions of the body prevent an increase in blood pressure. The above mentioned examples clearly indicate that in order to obtain a knowledge of the dynamics of the circulation in hypertension it is essential that *several* of the circulatory functions should be measured *simultaneously*.

PLAN OF INVESTIGATION AND METHODS USED

Eleven of the patients with hypertension studied comprised one group who were in good physical condition, with normal capacity for work (Table I). The high arterial blood pressure was discovered either accidentally, or during a physical examination undertaken because of the presence of subjective sensations. In another group, composed of sixteen patients, the muscular activities were limited because of dyspnea and weakness on moderate exertion (Table II). In both groups there was clinical evidence that peripheral arteriosclerosis was either absent or slight. The kidney function was normal in a majority of the patients. Observations were made additionally on three patients with primary chronic nephritis and secondary high blood pressure (Table III). None of the patients of any group exhibited signs of failure of the circulation while under observation.

The aspects of the circulation studied and the methods used were as follows: The arterial blood pressure was measured by the Riva Rocci method, using either a mercury sphygmomanometer with the auscultatory method, or the graphic recording device of Tycos. Often the two procedures were employed simultaneously. In our experience, in normal individuals and in a majority of patients with hypertension, the two methods give approximately identical results. There are patients with hypertension, however, in whom the pressure obtained with the graphic method is considerably higher. The arteriolar and the capillary pressures were estimated by a modified Recklinghausen technique.[5] The method of Moritz and Tabora[6] was employed to obtain the venous pressure. Measurement of the cardiac output per minute and per beat was made by the method of Field, Bock, Gildea and Lathrop[7]; seven alveolar air and mixed venous blood samples being obtained for each determination. We feel that for comparative measurements this method is reliable. Either the Tissot or the Benedict-Roth method was used in calculating the basal metabolic rate. The circulating blood volume was measured according to the technique described by Keith, Rowntree, and Geraghty.[8] Estimation of the arm to face circulation time was made with histamine.[9] The mean velocity of the entire circulation was calculated by dividing the circulating blood volume by the cardiac output per minute. All tests were performed in post absorptive state and with the patient in prone position.

RESULTS

Tables I, II and III contain the results of the measurements of the cardiac output per minute and per beat, the oxygen consumption and carbon dioxide output, and other related measurements on 30 patients with hypertension. On 16 of the patients repeated measurements were performed at different intervals. In all 68 measurements were made.

TABLE I

MEASUREMENTS OF THE RATE OF BLOOD FLOW, THE MINUTE VOLUME OF THE RESPIRATION, AND THE BASAL METABOLIC RATE IN PATIENTS WITH ARTERIAL HYPERTENSION HAVING NORMAL CARDIAC FUNCTION

PATIENT	DATE	AGE YEARS	ARTERIAL BLOOD PRESSURE			RESPIRATORY MINUTE VOLUME L.	CARBON DIOXIDE TENSION			CO_2 OUTPUT PER MINUTE C.C.	CARDIAC OUTPUT PER MINUTE L.	CARDIAC OUTPUT PER 100 C.C. O_2 CONSUMPTION L.	CARDIAC OUTPUT PER BEAT C.C.	RESPIRATORY QUOTIENT	METABOLISM	
			PULSE RATE PER MIN.	SYSTOLIC MM. HG.	DIASTOLIC MM. HG.		ALVEOLAR MM. HG.	VIRTUAL VENOUS MM. HG.	DIFFERENCE MM. HG.						PER CENT	CAL./HR./SQ.M.
1	9/14/28	47	55	175	106	8.1	35.9	43.0	7.1	181	5.9	2.6	108			
	9/17/28		59	176	101	8.6	34.2	43.6	9.4	207	5.1	2.0	86			
	9/18/28		66	156	95	12.4	35.1	44.6	9.5	273	6.6	2.2	96	0.922	+18.9	45.8
	9/20/28		64	147	84	12.8	36.8	46.3	9.5	325	7.7	2.2	119	0.953	+39.9	53.9
			63	142	82	11.8	38.5	47.2	8.7	273	7.2	2.4	112	0.920	+22.2	47.0
2	9/29/28	17	77	168	114	7.4	41.8	49.0	7.2	225	7.6	2.8	99	0.811	+ 1.9	43.8
			75	167	120	7.8	41.7	48.9	7.2	219	7.4	2.8	99	0.823	+ 0.3	43.1
3	11/ 6/28	41	83	184	125	5.0	40.7	47.2	6.5	146	5.4	2.9	64	0.785	+11.4	40.1
			80	200	130	5.7	39.3	47.2	7.9	139	4.1	2.3	51	0.778	+ 7.2	38.6
4	12/17/28	41	107	270	160	6.5	36.0	43.1	7.1	172	5.5	2.5	51	0.793	+18.0	42.5
			109			5.2	35.3	41.9	6.6	135	4.7	2.9	44			
5	2/11/29	54	87	175	90	7.5	42.7	50.2	7.5	272	8.9	2.7	102	0.836	+50.0	52.6
6	2/19/29	51	89	205	110	6.6	43.8	49.8	6.0	210	8.7	3.3	98	0.792	+25.7	44.0
7	3/ 6/29	31	97	220	120	8.8	32.2	41.3	9.1	244	5.6	1.9	58	0.812	+48.5	54.2
	3/14/29		94	230	120	8.2	32.2	41.6	9.4	196	4.3	1.6	46	0.734	+32.2	48.2
	3/21/29		74	220	130	11.2	24.3	30.9	6.6	231	7.5	2.9	102	0.885	+28.1	46.7
8	4/17/29	55	86	235	125	4.7	39.0	47.8	8.8	126	3.4	2.2	39	0.796	−18.7	30.5
9	5/15/29	50	78	170	110	7.2	41.1	49.3	8.2	271	8.0	2.7	103	0.906	+22.5	45.9
10	6/20/29	48	76	222	125	6.5	33.5	43.6	10.1	170	3.4	1.6	48	0.820	+ 2.5	39.5
11	9/ 6/29	34	74	180	105	6.8	34.1	40.1	6.0	213	8.0	2.8	108	0.739	+18.4	43.2

Table II

Measurements of the Rate of Blood Flow, the Minute Volume of the Respiration, and the Basal Metabolic Rate in Patients With Arterial Hypertension Having Impaired Cardiac Function

Patient	Date	Age years	Arterial blood pressure			Respiratory minute volume L.	Carbon dioxide tension			CO_2 output per minute c.c.	Cardiac output per minute L.	Cardiac output per 100 c.c. O_2 consumption L.	Cardiac output per beat c.c.	Respiratory quotient	Metabolism	
			Pulse rate per min.	Systolic mm. Hg.	Diastolic mm. Hg.		Alveolar mm. Hg.	Virtual venous mm. Hg.	Difference mm. Hg.						Per cent	Cal./hr./sq.m.
12	8/29/28	54	94	218	148	8.6	37.9	44.6	6.7	226	8.3		86			
	8/31/28		85	180	130	7.6	38.0	45.6	7.6	183	5.9	2.3	69	0.720	+11.4	41.8
	9/ 3/28		85	195	139	7.5	37.6	44.1	6.5	188	6.7	2.7	78	0.762	+10.1	41.3
13	9/ 5/28	58	80	163	102	6.0	39.4	45.4	6.0	157	6.2	2.9	77	0.741	− 2.1	36.7
			84	156	97	6.3	37.4	44.6	7.2	161	5.2	2.5	62	0.758	− 1.1	37.1
	9/ 8/28		84	156	97	5.5	39.3	47.8	8.5	153	4.3	2.1	52	0.723	− 1.9	36.8
			82	154	97	6.5	40.4	47.7	7.3	164	5.5	2.5	66	0.721	+ 0.8	37.8
14	9/22/28	49	72	192	120	8.3	38.9	47.5	8.6	245	6.9	2.4	95	0.875	+15.5	44.5
			75	183	118	7.0	38.8	47.7	8.9	216	5.8	2.3	78	0.882	− 0.3	38.4
	9/25/28		68	182	117	8.2	41.3	50.1	8.8	223	6.1	2.5	90	0.922	− 1.8	37.8
			67	172	112	7.4	41.1	50.5	9.4	207	5.2	2.3	80	0.920	− 9.6	34.8
	9/28/28		66	190	117	7.7	39.3	47.1	7.8	210	6.5	2.6	100	0.833	+ 1.8	39.2
			63	188	118	6.8	38.3	47.4	9.1	184	4.8	2.1	77	0.790	− 5.5	36.4
	10/30/28		77	190	100	7.9	40.9	50.6	9.7	231	5.7	2.2	74	0.890	+ 4.9	40.4
	11/ 1/28		75	178	116	7.7	41.3	50.9	9.6	214	5.3	2.1	71	0.828	+ 3.6	39.9
15	10/ 2/28	55	50	237	137	5.0	39.9	46.4	6.5	139	5.2	3.2	104	0.843	−19.6	28.1
			54	227	130	5.2	38.6	46.1	7.5	148	4.6	2.5	85	0.803	− 8.9	31.9
	10/ 3/28		47	193	115	5.0	37.3	44.7	7.4	130	4.1	2.6	87	0.824	−23.1	26.9
			48	193	115	4.5	37.9	45.1	7.2	117	3.8	2.7	79	0.812	−30.0	24.5

TABLE II—CONT'D

PATIENT	DATE	AGE YEARS	ARTERIAL BLOOD PRESSURE: PULSE RATE PER MIN.	ARTERIAL BLOOD PRESSURE: SYSTOLIC MM. HG.	ARTERIAL BLOOD PRESSURE: DIASTOLIC MM. HG.	RESPIRATORY MINUTE VOLUME L.	CARBON DIOXIDE TENSION: ALVEOLAR MM. HG.	CARBON DIOXIDE TENSION: VIRTUAL VENOUS MM. HG.	CARBON DIOXIDE TENSION: DIFFERENCE MM. HG.	CO_2 OUTPUT PER MINUTE C.C.	CARDIAC OUTPUT PER MINUTE L.	CARDIAC OUTPUT PER 100 C.C. O_2 CONSUMPTION L.	CARDIAC OUTPUT PER BEAT C.C.	METABOLISM: RESPIRATORY QUOTIENT	METABOLISM: PER CENT	METABOLISM: CAL./HR./SQ.M.
16	10/10/28	58	73	181	115	8.1	35.3	44.0	8.7	187	5.0	2.2	68	0.838	+ 2.9	38.6
			71	189	118	7.0	36.7	44.4	7.7	176	5.3	2.5	74	0.820	- 0.8	37.2
	10/15/28		72	178	115	8.1	36.5	46.5	10.0	221	5.3	1.9	75	0.800	+29.0	48.4
			72	182	116	7.4	37.5	45.0	7.5	199	6.2	2.4	85	0.760	+21.8	45.7
	10/23/28		75	181	112	6.7	36.7	44.8	8.1	200	5.8	2.5	78	0.862	+ 7.5	40.3
	10/25/28		68	180	112	6.0	36.4	45.0	8.6	182	4.9	2.5	72	0.922	- 6.9	34.9
	10/27/28		70	182	110	7.5	35.4	44.1	8.7	198	5.3	4.2	76			
17	11/ 5/28	77	32	270	65	8.1	33.0	39.5	6.5	138	4.5	2.4	142	0.725	- 3.9	34.1
	11/ 7/28		33	265	70	8.4	32.5	39.6	7.1	154	4.6	2.3	141	0.780	- 1.7	34.9
18	3/15/29	41	86	160	90	9.2	37.2	44.1	6.9	180	6.2	2.4	72	0.711	+15.3	41.5
	4/ 1/29		73	170	105	9.9	35.0	41.2	6.2	199	7.3	3.3	100	0.894	+ 1.1	36.4
19	3/19/29	48	100	210	112	6.5	44.2	54.0	9.8	198	4.8	1.8	48	0.725	+45.1	52.2
	3/23/29		84	204	112	6.5	38.3	47.5	9.2	169	4.4	1.8	53	0.685	+31.1	47.3
	5/28/29		90	250	135	5.8	38.0	50.0	12.0	166	3.3	1.5	36	0.744	+20.7	43.4
20	4/ 6/29	55	59	210	100	7.9	31.1	40.8	9.7	147	3.2	1.8	54	0.838	+ 7.1	37.5
21	4/16/29	39	74	218	115	5.9	39.7	48.0	8.3	167	4.9	2.3	66	0.774	- 3.0	35.4
	4/18/29		67	230	130	6.7	38.7	47.9	9.2	195	5.1	2.1	77	0.813	+ 7.4	39.2
22	4/29/29	18	101	170	112	8.8	45.2	53.1	7.9	234	7.1	2.9	71	0.940	+31.0	49.8
23	5/21/29	60	66	285	140	6.0	42.7	49.8	7.1	177	6.1	2.7	93	0.784	+ 7.1	36.4
	5/24/29		62	256	116	5.5	42.6	49.3	6.7	153	5.6	2.6	90	0.719	+ 1.0	34.3
24	6/ 5/29	65	81	241	120	8.5	35.9	43.7	7.8	214	6.3	2.5	78	0.849	+15.1	42.0
25	7/ 3/29	55	63	225	100	9.0	37.5	48.8	11.3	190	4.0	1.6	64	0.742	+ 5.5	39.5
26	7/ 9/29	55	68	182	98	7.9	42.5	49.3	6.8	211	7.6	2.8	111	0.786	+11.2	41.7
27	7/16/29	59	70	220	120	7.9	37.4	48.5	11.1	198	4.2	1.7	60	0.778	+18.1	44.3

Table IV presents the averaged data for the three groups of patients and the group of normal subjects. The average cardiac output of the hypertensive patients with normal cardiac function was identical with that of the normal group although the maximal variations were greater in the group of hypertensive patients. Considerable difference was found in the output of the various patients and also in the same patient at different times. The observations showed no definite correlation between the blood pressure and the cardiac output. Although the average cardiac output per minute was 1.0 liter lower in patients with impaired cardiac reserve than in patients with normal capacity for work, nevertheless, this difference in blood flow was less when the cardiac output was calculated per 100 c.c. of oxygen consumed. The difference between the alveolar and venous carbon dioxide tension, in its relation to the rate of blood flow, is an important index of the efficiency of the circulation. The average difference between the alveolar and virtual venous carbon dioxide tension was the same in the normal subjects and in patients with normal functional capacity. It is of interest that while the average cardiac output of the patients with impaired function was lower than normal, the carbon dioxide transportation was higher. The blood flow corresponding to the consumption of 100 c.c. of oxygen was 2.4 liters, while it was 2.7 liters in 13 control normal individuals. In some of the patients with increased basal metabolism the rate of blood flow per 100 c.c. of oxygen consumed was even lower. It was 1.8 and 1.5 liters in patient 19.

The average rate of the exchange of blood gases in the capillaries was increased in the patients with lowered cardiac reserve in comparison with the patients with a normal heart function. A similar behavior has been noted[10] in patients with rheumatic heart disease. Table V presents data concerning the circulatory blood volume, the mean velocity of the circulation, and the arm to face circulation time in the presence of hypertension. The circulating blood volume was within normal limits in patients with hypertension regardless of whether the functional capacity of the patient was normal or moderately limited. The mean velocity of the circulation was either within or slightly above the upper limit of normal.

The respiratory minute volume as indicated in Tables I, II, III and IV was normal; the respiratory rate was also normal. The average tidal air volume was 448 c.c. in the group of normal subjects, 419 c.c. in the group of patients with normal function, and 394 c.c. in the group with impaired function. We did not observe hypoventilation in hypertension as suggested by Rappaport.[11] The oxygen consumption was normal—that is to say, below + 15 per cent of basal metabolism in 19 patients, and was elevated in 11 patients.

Table VI presents the gradient of pressure from the arteries to the arterioles, capillaries and veins. Abnormally high pressure was found

TABLE III

MEASUREMENTS OF THE RATE OF BLOOD FLOW, THE MINUTE VOLUME OF THE RESPIRATION, AND THE BASAL METABOLIC RATE IN PATIENTS WITH ARTERIAL HYPERTENSION AND CHRONIC NEPHRITIS

PATIENT	DATE	AGE YEARS	ARTERIAL BLOOD PRESSURE			RESPIRATORY MINUTE VOLUME L.	CARBON DIOXIDE TENSION			CO_2 OUTPUT PER MINUTE C.C.	CARDIAC OUTPUT PER MINUTE L.	CARDIAC OUTPUT PER 100 C.C. O_2 CONSUMPTION L.	CARDIAC OUTPUT PER BEAT C.C.	RESPIRATORY QUOTIENT	METABOLISM	
			PULSE RATE PER MIN.	SYSTOLIC MM. HG.	DIASTOLIC MM. HG.		ALVEOLAR MM. HG.	VIRTUAL VENOUS MM. HG.	DIFFERENCE MM. HG.						PER CENT	CAL./HR./SQ.M.
28	10/19/28	17	106	224	160	8.5	30.2	37.6	7.4	173	4.9	2.3	46	0.846	+10.0	44.0
			102	224	160	9.0	30.4	37.1	6.7	183	5.8	2.6	57	0.808	+17.2	46.9
29	2/16/29	29	105	230	140	6.9	35.6	42.2	6.6	180	6.2	3.1	59	0.916	+ 4.7	38.6
	2/18/29		90	250	145	8.0	34.0	43.2	9.2	169	3.8	1.8	42	0.829	+ 8.4	40.1
	2/26/29		100	164	110	6.4	34.1	43.6	9.5	151	3.5	1.8	35	0.792	+ 1.7	37.6
30	2/28/29	28	89	210	130	6.7	32.4	40.3	7.9	173	4.6	2.0	51	0.744	+19.7	44.3

TABLE IV

THE AVERAGE RATE OF BLOOD FLOW, THE MINUTE VOLUME OF THE RESPIRATION, AND THE BASAL METABOLIC RATE IN THE THREE GROUPS OF PATIENTS WITH ARTERIAL HYPERTENSION AND IN A GROUP OF CONTROL SUBJECTS

	AGE YEARS	ARTERIAL BLOOD PRESSURE		RESPIRATORY MINUTE VOLUME L.	CO_2 TENSION VIRTUAL VENOUS-ALVEOLAR MM. HG.	CARDIAC OUTPUT PER MINUTE L.	CARDIAC OUTPUT PER 100 C.C. O_2 CONSUMPTION L.	CARDIAC OUTPUT PER BEAT C.C.	METABOLISM	
		SYSTOLIC MM. HG.	DIASTOLIC MM. HG.						PER CENT	CAL/HR./SQ. M.
Arterial Hypertension with Normal Functional Capacity (11 Cases)	43	200	117	7.1	7.7	6.4	2.5	80	+17.6	43.6
Arterial Hypertension with Impaired Functional Capacity (16 Cases)	53	208	112	7.5	8.3	5.4	2.4	79	+ 8.2	39.8
Chronic Nephritis (3 Cases)	25	216	141	7.5	7.8	4.8	2.2	49	+12.7	42.8
Control Subjects (13 Cases)	27	106	69	6.7	7.7	6.4	2.7	97	+ 1.0	39.3

TABLE V

THE CIRCULATING BLOOD VOLUME, THE MEAN VELOCITY, AND THE ARM TO FACE VELOCITY OF THE CIRCULATION IN PATIENTS WITH ARTERIAL HYPERTENSION

PATIENT	DATE	WEIGHT KG.	HEMATOCRIT	PLASMA VOLUME C.C.	BLOOD VOLUME C.C.	BLOOD VOLUME PER CENT BODY WT.	MEAN VELOCITY SEC.	ARM-FACE VELOCITY SEC.	FUNCTIONAL CAPACITY
12	10/ 2/28	68.2	44.6	3309	5969	8.78	57		Impaired
13	10/ 4/28	61.4	37.9	2785	4485	7.95	51		Impaired
			41.6	2520	4370	7.13	49		
14	10/11/28	75.0	48.3	2946	5698	7.50	59		Impaired
	11/ 5/28		48.4	2513	4965	6.50	52		
2	10/ 5/28	61.3	40.9	3122	5264	8.53	42		Normal
15	10/ 2/28	64.1	42.8	2647	4632	7.13	63		Impaired
16	10/11/28	62.7	37.3	3415	5439	8.53	61		Impaired
17	11/ 5/28	55.9	35.3	2480	3865	6.93	51		Impaired
3	11/ 6/28	40.9	39.8	1987	3300	8.05	42		Normal
4	12/17/28	47.3	45.0	2525	4585	9.60	54	35	Normal
5	2/13/29	79.0	38.1	3015	4975	6.30	33		Normal
29	2/17/29	50.0	24.3	2170	2870	5.73	38		Impaired
	4/12/29	50.0	35.5	2315	3585	7.17	48		
6	2/19/29	65.5	38.4	3010	4890	7.48	34		Normal
30	2/28/29	50.0	30.1	2690	3900	7.80	51	20	Impaired
7	3/14/29	59.0	40.0	2020	3365	5.70	40		Normal
18	3/15/29	73.7	46.6	2040	3830	5.20	34	24	Impaired
19	3/19/29	50.9	47.5	2180	4155	8.16	58	26	Impaired
20	4/15/29	47.7	42.1	2220	3835	8.02	77		Impaired
21	4/16/29	78.2	44.6	2440	4400	5.63	53		Impaired
8	4/17/29	49.5	46.0	2060	3820	7.67	67		Normal
22	4/29/29	47.7	48.6	2100	4100	8.59	35		Impaired
9	5/15/29	77.2	46.5	2520	4705	6.10	35	21	Normal
23	5/21/29	70.5	46.0	2135	3960	5.62	40		Impaired
31	10/16/28	73.4	47.0	3430	6470	8.45			Impaired
32	10/24/28	66.0	41.2	2750	4675	7.20			Impaired
Average					4448	7.34	49	25	
Average	Normal				5800	8.30	43	24	

to exist in the arteries and arterioles, whereas the pressure in the capillaries and veins was within the normal range. As has been noted before,[5] there is an abnormally great resistance in the arteriolar circuit of patients having arterial hypertension with high diastolic pressure.

DISCUSSION

A. *The Localization of the Peripheral Resistance in Arterial Hypertension.* In the presence of arterial hypertension a disproportion must exist between the cardiac output and the resistance offered the flow of blood through the peripheral vascular bed. Such disproportion may develop either because of increase in cardiac output and velocity of blood flow or because of change in the peripheral resistance. The findings presented above are in agreement with the findings of Lauter and Baumann[12] and Burwell and Smith,[13] but contrary to the observations of Liljestrand and Stenstrom[14] and Hayasaka.[15] They indicate that the cardiac output in the presence of high blood pressure is not above the upper limit of normal. According to our findings the cardiac output and the mean velocity of the circulation may be below normal in certain patients with apparently normal cardiac reserve. In the causation of hypertension, therefore, the disproportion is due to changes in the peripheral vascular bed. Whatever the nature of the morphological or functional vascular changes responsible for the development of high blood pressure may be, they must involve important and extensive areas. Changes in the larger or smaller vessels of a single organ alone cannot produce hypertension. It has been suggested[4] as a result of post-mortem studies of blood vessels that one of the important etiological factors in the causation of hypertension is the loss of elasticity of the walls of the larger arteries. It has been claimed[16, 17, 18, 19] that the active contractions or elastic rebound of the larger arteries during diastole plays an important rôle in the propulsion of blood. With the loss or reduction of the normal elasticity of the arteries, a compensatory higher initial blood pressure is essential to carry the blood through the capillary system with the optimal pressure and velocity. If this conception is correct, it would follow also, that the pressure in the precapillary vessels (arterioles) should be the same in hypertension as it is in normal individuals; or that an abnormally high pressure gradient should exist between the aorta and large arteries and the arterioles. This, however, is not the case. In a previous study[5] and in Table VI we have submitted evidence that in essential hypertension without marked arteriosclerosis, the abnormal fall in pressure is not between the large arteries and arterioles, but between the arterioles and the capillaries. In addition, we have shown that in normal individuals it is also between the arterioles and capillaries that the marked fall of pressure occurs. The drop in pressure may be as great as 80 mm. Hg. in normal individuals and 150 mm. Hg. in patients with hypertension. This finding is in harmony with the

observations of Landis[20, 21] that in the mesentery of the frog and of certain mammals the most significant peripheral resistance is offered by the arteriolar system, including the arteriolar ends of the capillaries.

The conception that the gradient of pressure between the arteriolar and capillary systems is abnormally high in arterial hypertension leads inevitably to the conclusion that the immediate cause of hypertension is an abnormal *accentuation of the normal physiological resistance of the arteriolar system.* This conclusion, of course, does not reveal the factors responsible for the increased arteriolar resistance.

TABLE VI

THE ARTERIAL, ARTERIOLAR, CAPILLARY AND VENOUS PRESSURES IN PATIENTS WITH ARTERIAL HYPERTENSION

PATIENT	DATE	ARTERIAL BLOOD PRESSURE SYST. MM. HG.	ARTERIAL BLOOD PRESSURE DIAST. MM. HG.	ARTERIOLAR PRESSURE MM. HG.	CAPILLARY PRESSURE MM. HG.	VENOUS PRESSURE MM. HG.	FUNCTIONAL CAPACITY
12	9/27/28	214	140	165	14	+ 6	Impaired
13	9/26/28	158	110	120	8	+ 5	Impaired
1	9/25/28	170	96	75	11		Normal
14	9/24/28	206	114	150	8	+ 2	Impaired
2	10/27/28	180	124	100	11	+ 8	Normal
16	10/11/28	184	118	100	13	+ 5	Impaired
17	11/ 5/28	270	65	130	9	+ 7	Impaired
3	11/ 6/28	180	120	150	11	+ 5	Normal
4	12/17/28	280	160	150	9	+ 9	Normal
30	2/28/29	210	130	90	21	+ 4	Impaired
18	3/15/29	160	90	110	14	+ 6	Impaired
7	3/18/29	230	120	130	11		Normal
19	3/19/29	210	112	110	12	+ 4	Impaired
20	4/15/29	215	90	120	18	+12	Impaired
21	4/24/29	185	120	110	12	+12	Impaired
9	5/15/29	170	110	130	14	+ 6	Normal
15	10/ 2/28	220	115			+ 5	Impaired
29	2/16/29	230	140	120	7	+ 2	Impaired
Average		204	115	121	12	+ 6	
Average	Normal	126	64	55	8	+ 5	

B. *The Quantitative Aspect of the Arteriolar (Precapillary) Resistance in Arterial Hypertension.* In a rigid tubing system the relationship between pressure and stream is expressed according to Poiseuille's law,[22] which states that the amount of fluid streaming through a narrow tube is directly proportional to the fourth potential of the cross sectional area and to the pressure of the fluid; and indirectly proportional to the length of the tube.

$$V = \frac{K.P.D^4}{L}$$

V signifies the amount of fluid flowing through the tube in a unit of time; P, the pressure of the fluid; D, the cross sectional area of the tube; L, the length of the tube; K, a constant. Although, as Tiger-

stedt[23] has pointed out, it is questionable whether this law can be rigidly applied to the circulation, the error involved in such application cannot be large enough to change the general significance of the conclusions. If one considers that, as observed, the circulating blood volume in cases with hypertension is within normal limits, L, the length of the arterioles, is essentially unchanged; and V, the amount of fluid circulating through the vessels in a unit of time, is either normal or below normal—then it follows that because P, the arteriolar pressure, is high, D, the value for the cross sectional area of the arteriolar bed in hypertension, is smaller than in the normal condition.

In the causation of altered peripheral resistance of the circulation in hypertension, this change in the cross sectional area may well play the important rôle, for other factors, such as the relation between the blood stroma and plasma, as well as the viscosity of blood and the circulating blood volume, show no change from normal. If we, therefore, consider that the resistance of a tube system is directly proportionate to the length of the tube and indirectly to the cross section, it follows that the resistance being R:

$$R = \frac{P}{V}$$

According to our findings, the average mean blood pressure in the patients with arterial hypertension was 160 mm. Hg. (it ranged from 112 to 215). The average cardiac output was 5.8 liters. These findings would correspond to a resistance which may be expressed with an index of $\frac{160}{58} = 2.8$. In thirteen normal individuals, the average mean blood pressure was 87 mm. Hg. (it ranged from 62 to 114) and the average cardiac output was 6.4 liters, indicating a resistance index of $\frac{87}{64} = 1.3$. The peripheral circulation thus offered a resistance against the cardiac work which was about twice as great in the group of patients with hypertension as that present in normal individuals.

C. *The Cardiac Work in Arterial Hypertension.* As has been recognized[24] the cardiac energy required for maintenance of the velocity of blood flow at rest is slight (about 0.3 per cent of the total energy), as compared with the cardiac energy essential to overcome the peripheral resistance of the vessels. The velocity factor in the cardiac work, $\frac{W.V^2}{2\ G}$ (W representing the weight of the volume ejected; V, the mean velocity at the root of the aorta; and G, acceleration due to gravity), is negligible and the work of the heart, therefore, can be approximately estimated by the formula K.V.R in which V is the volume output of the heart; R, the mean peripheral or pulmonary arterial resistance in meters of blood, depending on whether the work of the left or the right side of the heart is calculated; and K, the specific gravity of

mercury. According to Frank[25] this method of calculation may involve an error of about 10 per cent. In view of the fact, however, that a more exact determination of the cardiac work in man is not available, this objection is only of theoretical significance. Therefore, assuming that the mean aortic pressure is 10 mm. higher than the brachial arterial pressure, the average work of the left side of the heart of the normal subjects studied is 8.38 Kg. m. per minute or 127 gm. m. per stroke. The work of the right side is about one-third of that of the left side. Inasmuch as skeletal muscle and the mammalian heart utilize only 20 to 25 per cent of the total energy for effective work[26] one may assume that the calories used by the heart of normal individuals must be about 4.5 times greater than the calories transposed into work; that is, the caloric consumption of the left side of the heart is 128 calories or 7.6 per cent of the caloric need for the total body metabolism.

Assuming that the relative fall of pressure from the aorta to the brachial artery in hypertension without marked arteriosclerosis is not greater than in the normal state,—an assumption justified from our previous observation[5] that the fall in pressure from the brachial artery to the arterioles of the skin is the same in hypertension as in normal conditions—it would follow that the work of the left side of the heart in the average hypertensive patient is 13.3 Kg. m. per minute, or 184 gm. m. per beat, and 798 Kg. m. per hour. This corresponds to about 45 calories per day; and if the normal and hypertensive patient's heart works with the same efficiency, it would follow that the caloric consumption of the left side of the heart in hypertension is about 202 calories or 10.7 per cent of the total metabolism.

The pressure in the pulmonary artery in patients with hypertension and normal cardiac function is not known. Certain morphological evidence, namely, the absence of arteriosclerosis in the pulmonary circuit[27] and the frequent lack of muscular hypertrophy of the right ventricle,[28] suggests that the pressure in the lesser circulation is essentially normal. Accordingly, the work of the right side of the heart in hypertension is not increased to any degree. The average work of the heart in arterial hypertension is therefore about 41 per cent higher than in normal individuals, although the peripheral resistance of the greater circuit is increased over 100 per cent. Whether or not the caloric requirement of the cardiac work is proportional to this increase in work depends on the comparative efficiency of the musculature of normal subjects and patients with arterial hypertension. The available evidence suggests that the economy of the work of the mammalian heart is below normal in the presence of acutely induced arterial hypertension.[29] In patients with hypertension the economy of the cardiac work cannot be studied at present.

D. *The Basal Metabolism and the Rate of Blood Flow in Arterial Hypertension.* The cause of the high basal metabolism observed in several of the patients is not clear. These patients showed symptoms of an abnormally active sympathetic nervous system: namely, shiny, slightly protruding eyes, wide pupils, a tendency to flush and perspire easily and to become disturbed or excited from trivial causes. In some, there was a slightly enlarged thyroid gland. In these patients with arterial hypertension and increased metabolism, in contrast to the usual hyperthyroid patients, the pulse rate, the velocity and the amount of blood flow were not increased in proportion to the metabolism. In cases 7, 19 and 27 the rate of blood flow was even below normal. Increased peripheral resistance may be responsible for the marked difference in the dynamics of the circulation between the patients with hypertension and high basal metabolic rate and patients with hyperthyroidism, high basal metabolic rate and normal blood pressure. Whether the increase in the peripheral resistance can be considered as a regulatory mechanism to prevent increased blood flow and increased cardiac rate in these patients can not be stated.

The clinical course of case 19 indicates that the metabolism may return to normal without change in the blood pressure. This patient showed a basal metabolism between 20 and 45 per cent above normal on repeated occasions. Further, besides clinical manifestations of hyperthyroidism, she showed a large firm thyroid gland so that a resection of the gland was performed. Following the operation the metabolism became normal and the patient's health improved distinctly. The systolic blood pressure, nevertheless, was 270 mm. Hg. and the diastolic pressure 140 mm. Hg., seven months after the operation.

E. *The Amount of Blood in the Lungs in the Presence of High Arterial Pressure.* The lesser circulation with its abundant capillary bed has an important influence on the function of the left ventricle and on the blood flow in the greater circulation. As stated by Starling:[30] "The distensibility of the lung capillaries may play an important part in enabling the lungs to act, so to speak, as a reservoir for the left side of the heart." Although the amount of blood in the lungs in the presence of hypertension is not known, it has been suggested that the reduced blood content of the lungs may be responsible for the elevated pressure in the peripheral arteries.[11]

The observations of G. N. Stewart on animals[31] and of Blumgart and Weiss[32, 33] on man indicate that the pulmonary circulation time is an index of the mean pulmonary velocity. According to the former investigator[31] the quantity of blood in the lungs, Q, equals $\frac{V.T}{60}$ where V is the volume of blood flow through the lungs per minute and T the mean pulmonary blood velocity in seconds. Measurements of the minute volume flow through the lungs and the pulmonary circulation time in

the same individuals by Blumgart and Weiss indicate that the calculated blood in the lungs was 884 c.c. or approximately 21 per cent of the total blood volume, when the average cardiac output was 7.6 liters and the average actual pulmonary circulation time was 8 seconds. In a larger series of normal subjects the actual pulmonary circulation time was 6.5 seconds.[32] Taking the average cardiac output, 6.38 liters, it was estimated that the amount of blood in the lungs was 589 c.c. or 11 per cent of the total blood volume. Considering that the average cardiac output was 6.4 liters in the control subjects, 589 c.c. is probably the approximate average amount of blood in the lungs of the normal group studied by us.

The average flow of blood through the lungs of patients with high blood pressure and normal cardiac function was 6.4 liters, the average circulating blood volume in the patients with normal function was 4363 c.c. or 7.5 per cent of the body weight. The average pulmonary circulation time in a group of 12 hypertensive patients with normal circulatory function was 10 seconds.[34] The amount of blood calculated according to the above formula is 1063 c.c. or about 24 per cent of the total blood volume. The amount of blood in the lungs of patients with hypertension and normal functional capacity is therefore greater than that of normal control individuals. These observations do not lend support to the hypothesis that reduced capillary bed of the lesser circulation is responsible for the development of high arterial blood pressure. Therefore, neither decreased volume of blood in the lungs nor altered respiration can be held responsible for the development of high arterial blood pressure.

The finding of relatively high blood content of the lungs in patients with arterial hypertension is in harmony with observations on animals. Führer and Starling[35] working with the heart-lung preparation noted that every elevation of the systemic pressure produced increase of pressure in the left auricle and in the pulmonary artery. Coetta and Stäubli[36] found that compression of the thoracic portion of the aorta was associated with increased blood volume and elevation of the pulmonary pressure. Wiggers[37] and Katz and Wiggers[38] in carefully controlled experiments observed normal or but slightly elevated pulmonary pressure. However, moderate increase in the blood content of the pulmonary vessels as present in hypertension does not necessarily indicate increase in pressure, and therefore the above finding does not give any indication as to whether or not in man the pressure in the lesser circulation is elevated.

As observed in a previous study[34] the average *vital capacity* of the lungs in patients with hypertension was lower than the average normal value although their capacity for work was not reduced. So the average vital capacity of patients with normal functional capacity was 1900 c.c. per square meter of body surface instead of the normal 2500

c.c. per square meter of body surface. In view of the fact that the amount of blood in the lungs of patients with normal functional capacity is increased, this increased blood content of the lungs in hypertension may be one of the factors responsible for the reduction of the vital capacity.

F. *The Significance of the Observations Presented on the Problem of the Therapy of Hypertension.* According to the evidence presented, the most significant difference between the circulation of the patients and of the normal subjects is in the resistance offered by the arteriolar system and in the arterial and arteriolar pressure of the greater circulation. Notwithstanding the presence of high arteriolar resistance, the mean velocity of the circulation and the amount of blood flowing through the capillary bed per unit of time, as well as the capillary pressure are normal. Considering that the total circulating blood volume and the pressure in the venous system is normal, because the blood volume of the lungs is increased, the volume of the blood in the arterial and capillary system is smaller than in normal individuals. It is by the aid of increased pressure in the arterial system that the heart reinstates the normal capillary flow and pressure. This reestablishment of normal capillary circulation is achieved with great economy as far as cardiac work and peripheral circulation are concerned. With the exception of the high basal metabolism occasionally observed, we have noted no bodily functions which may be considered, *a priori*, as uneconomical or superfluous. If the high basal metabolism associated with hypertension is due to primary hyperfunction of the thyroid gland and is not secondary to the high blood pressure, then, as has been pointed out, the circulation functions with better economy in these patients than in hyperthyroid patients with normal blood pressure.

As indicated above, there must be a definite relationship between pressure and volume of blood flow corresponding to a given increased peripheral resistance. $R = \frac{P}{V}$. Therefore, if the peripheral resistance could be measured directly, assuming that the normal or slightly subnormal minute volume approximates the optimal for physiological needs, then one could foretell the optimal blood pressure required for an abnormally high resistance. If the heart can not throw out the normal amount of blood, V becomes smaller and, correspondingly, if the resistance is unchanged, P will fall. Under such conditions the blood circulates through the vital organs in such a way that its volume flow and pressure are both less than the optimal, and unless the capillary circulation is able to compensate for the cardiac failure, serious disturbances develop in the function of the body. The onset of circulatory disturbances occurs at different arterial pressure levels for different patients, depending on the degree of increase in the peripheral

resistance. The findings and discussion presented above offer a rational explanation of the weakness, dizziness, choking sensation and other symptoms and signs of incompetent circulation felt by patients with the onset of a decrease from the optimal blood pressure.[39] Unless, therefore, the cardiac output is known, the significance of a fall in blood pressure following therapeutic procedures can not be judged. The administration of therapeutic agents in hypertension should be combined with quantitative measurements of the circulation of patients before and after treatment. Only by such measurements will harm to the patient be averted. Without a corresponding reduction in the peripheral resistance, reduction of the blood pressure should not be an aim in the treatment of hypertension. Because the volume and velocity of blood flow are never above normal in hypertension, the therapeutic efforts should be directed either toward the maintenance of the optimal blood pressure and volume flow for a given abnormally high peripheral resistance, or toward the reduction of the blood pressure through lowering the abnormal resistance. Therapeutic procedures that lower the blood pressure through decreased cardiac output are harmful. In patients in whom the resistance can not be altered (fixed hypertension), and whose pressure is distinctly below optimal, it is in the interest of the patient to reestablish higher arterial pressure, through the improvement of the cardiac function.

Thus there can be no uniform treatment for arterial hypertension. Progress in therapy can come only through study of the circulation of the individual patient. The knowledge gained in this will determine the proper selection of therapeutic measures, the rational application of which rests on logical pharmacological and therapeutic observations.

SUMMARY AND CONCLUSIONS

1. A study is presented of the circulatory mechanism in 30 patients with hypertension.

2. Although the average resistance of the arteriolar system of the greater circulation was twice as great in the patients as in the normal control subjects, the circulating blood volume, the cardiac output per minute, the arm to face velocity of the blood flow, and the mean velocity of the circulation were either normal or slightly below normal.

3. The calculated volume of blood in the lungs in hypertension is increased.

4. The volume content of the arterial and capillary bed of the greater circulation in hypertension is probably reduced.

5. Although the peripheral resistance was increased to twice normal, the estimated work of the left ventricle of the heart in hypertension was only 41 per cent greater than in normal subjects. This work corresponds to an energy consumption of 10.7 per cent of the basal metabolism.

6. Tissue nutrition in the presence of hypertension is accomplished with a distinct economy of the cardiac work and the various functions of the peripheral circulation.

7. In patients with hyperthyroidism and normal blood pressure, the heart rate, the cardiac output and the velocity of blood flow are increased in proportion to the increased basal metabolism; in certain patients with essential hypertension showing clinical evidence of overactivity of the autonomic nervous system, the heart rate, the cardiac output and velocity of blood flow may be within the limits of normal although the basal metabolism is increased.

8. The mechanism of circulation is similar in patients with primary nephritis and secondary hypertension to that in patients with primary hypertension.

9. A satisfactory explanation for the dynamics of the circulation in the patients with hypertension studied is that due to the abnormally accentuated arteriolar resistance, a high arterial and arteriolar pressure is essential to reestablish the normal capillary blood flow and pressure in the vital organs.

10. The measurements and observations do not bear out the hypothesis that loss of the elasticity of the great arteries, or increased cardiac output, or increased circulating blood volume, or hypoventilation and decreased blood content of the lungs is responsible for the presence of hypertension.

11. The relationship between cardiac output, arterial pressure, peripheral resistance and capillary circulation determines the nature of the therapeutic procedures applicable in hypertension.

We take pleasure in expressing our appreciation of Miss Rose Shore's technical assistance in conducting this research.

BIBLIOGRAPHY

1. Johansson, J. E., and Tigerstedt, R.: Ueber die gegenseitigen Beziehungen des Herzens und der Gefässe, Skand. Arch. Physiol., **2**, 406, 1890.
2. Knowlton, F. P., and Starling, E. H.: The influence of variations in temperature and blood pressure on the performance of the isolated mammalian heart, J. Physiol., **44**, 206, 1912.
3. Straub, H.: Zur Dynamik der Klappenfehler des linken Herzens, Deutsch. Arch. klin. Med., **122**, 156, 1917.
4. Hochrein, M.: Ueber den Kreislaufmechanismus bei der Hypertension, Arch. f. exp. Pathol. u. Pharmacol., **133**, 325, 1928.
5. Ellis, L. B., and Weiss, Soma: The measurement of capillary pressure under natural conditions and after arteriolar dilatation; in normal subjects and in patients with arterial hypertension and with arteriosclerosis, J. Clin. Invest. **8**, 47, 1929.
6. Moritz, F., and Tabora, D. V.: Ueber ein Methode, beim Menschen den Druck in oberflächlichen Venen exact zu bestimmen, Deutsch. Arch. klin. Med., **98**, 475, 1910.
7. Field, H., Jr., Bock, A. V., Gildea, E. F., and Lathrop, F. L.: The rate of the circulation of the blood in normal resting individuals, J. Clin. Invest., **1**, 65, 1924.
8. Keith, N. M., Rowntree, L. E., and Geraghty, J. T.: A method for the determination of plasma and blood volume, Arch. Int. Med., **16**, 547, 1915.

9. Weiss, Soma, Robb, G. P., and Blumgart, H. L.: The velocity of blood flow in health and disease as measured by the effect of histamine on the minute vessels, AM. HEART J. **4**, 664, 1929.
10. Weiss, Soma, and Ellis, L. B.: Circulatory measurements in patients with rheumatic heart disease before and after the administration of digitalis, J. Clin. Invest. (In press.)
11. Rappaport, I.: Blood pressure and respiration: hyperventilation as a treatment for hypertension, J. A. M. A., **92**, 1158, 1929.
12. Lauter, S., and Baumann, H.: Ueber den Kreislauf bei Hochruck, Arteriosclerose, und Apoplexie, Zeitschr. klin. Med., **109**, 415, 1928.
13. Burwell, C. S., and Smith, W. C.: The output of the heart in patients with abnormal blood pressures, J. Clin. Invest., **7**, 1, 1929.
14. Liljestrand, G., and Stenström, N.: Work of heart during rest; blood flow in increased arterial blood pressure with influence of pregnancy on blood flow, Acta. Med. Scandinav., **63**, 142, 1925.
15. Hajasaka, E.: On the minute volume of the heart in hypertension, Tohoku J. Exper. Med., **9**, 401, 1927.
16. Fleisch, A.: Hanb. d. norm. u. path. Physiologie. A. Bethe, G. V. Bergmann, and G. Embden. Vol. 7, Part 2. Julius Springer, Berlin, 1928.
17. Meyer, O. B.: Ueber rhythmische Spontankontraktionen von Arterien, Ztschr. f. Biol., **61**, 275, 1913.
18. Mareŝ, F.: Der Allgemeine Blutstrom und die Foerderung der Blutdurchstroemung der Organe durch die Tätigkeit ihres Gefässystems. I. Foerderung des Blutstromes durch aktive Beteiligung der Gefässe am arteriellen Pulse, Arch. f. d. gesam. Physiol., **161**, 159, 1916.
Ibid, 194. II. Die Atembewegungen des Gefässystem.
Ibid, 337. III. Die Grundlage der herrschenden vasomotorischen Theorie.
Ibid, 381. IV. Mechanismus des Eigenbetriebs der Blutdurchströmung in Verschiedenen Organen.
19. Mareŝ, F.: Der Einfluss der Gefassnerven auf den Blutstrom, Deutsch. med. Wchnschr., **43**, 420, 1917.
20. Landis, E. M.: The capillary pressure in frog mesentery as determined by micro-injection methods, Am. J. Physiol., **75**, 548, 1925-26.
21. Landis, E. M.: Micro-injection studies of capillary pressure in mammalian mesentery, Am. J. Physiol., **85**, 387, 1928.
22. Poiseuille: Mém. présent. par divers savants à l'acad. des sciences, **9**, 433, 1846. Quoted by Tigerstedt (23).
23. Tigerstedt, E.: Die Physiologie des Kreislaufes, Vol. III, p. 35. Walter de Gruyter & Co., Berlin and Leipzig, 1922.
24. Evans, C. L.: The velocity factor in cardiac work, J. Physiol., **52**, 6, 1918.
25. Frank, O.: Die Grundformen des arteriellen Pulses, Zeitschr. f. Biol., **37**, 483, 1899.
26. Wiggers, Carl J.: Modern aspects of the circulation in health and disease. Lea and Febiger, Philadelphia and New York, Sec. Ed., 1923.
27. Moschcowitz, E.: The cause of arteriosclerosis, Am. J. Med. Sc., **178**, 244, 1929.
28. Weiss, Soma: Unpublished observations.
29. Wiggers, Carl J.: Die Pathologische Physiologie des Kreislaufes bei Klappenerkrankungen des Herzens, Ergebnisse der Physiologie, **29**, 250, 1929.
30. Starling, E. H.: Principles of human physiology. Philadelphia, Lea and Febiger, 1926.
31. Stewart, G. N.: The pulmonary circulation time, the quantity of blood in the lungs, and the output of the heart, Am. J. Physiol., **58**, 20, 1921.
32. Blumgart, H. L., and Weiss, Soma: Studies on the velocity of blood flow. VII. The pulmonary circulation time in normal resting individuals, J. Clin. Invest., **4**, 399, 1927.
33. Blumgart, H. L., and Weiss, Soma: Clinical studies on the velocity of blood flow. XI. The pulmonary circulation time, the minute volume blood flow through the lungs, and the quantity of blood in the lungs, J. Clin. Invest., **6**, 103, 1928.
34. Blumgart, H. L., and Weiss, Soma: Clinical studies on the velocity of blood flow. IX. The pulmonary circulation time, the velocity of venous blood flow to the heart, and related aspects of the circulation in patients with cardio-vascular disease, J. Clin. Invest., **5**, 343, 1928.

35. Führer, H., and Starling, E. H.: Experiments on the pulmonary circulation, J. Physiol., 47, 286, 1913.
36. Coetta, M., and Stäubli, C.: Beiträge zur Experimentellen Pathologie der Lungenzirkulation, Arch. f. Exp. Path. u. Pharm., 84, 317, 1919.
37. Wiggers, C. J.: Pressure pulses in the cardiovascular system. New York and London, Longmans, Green & Co., 1928.
38. Katz, L. N., and Wiggers, C. J.: The influence of high systemic blood pressures on the right ventricle and pulmonary circuit, Am. J. Physiol., 82, 91, 1927.
39. Weiss, Soma: The nature and management of cerebral hemiplegia in patients with arterial hypertension, Med. Clin. N. Am., 13, 111, 1929.

THE DISAPPEARANCE OF INTRAVENTRICULAR HEART-BLOCK OCCURRING IN UREMIA FOLLOWING THE INTRAVENOUS INJECTION OF HYPERTONIC GLUCOSE SOLUTION*

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THAT there are alterations in the cardiac muscle in uremia occurring in the course of nephritis is well known. The occurrence of pulsus alternans during this state has been observed.[1] Wood and White[2] studied the electrocardiograms of patients exhibiting symptoms of uremia. They found changes in the form of the T-wave in Lead II, less often abnormal rhythms, and rarely an increase in the auriculoventricular time interval or in the duration of the QRS complexes. They concluded that "in certain cases of uremia and severe nephritis with increased blood nitrogen there is a toxic effect acting in some respects like digitalis on the heart muscle, which may produce abnormal electrocardiograms."

Recently a patient under our care developed intraventricular heart-block while in the state of uremia. Shortly after the intravenous injection of hypertonic solution of glucose, the electrocardiogram changed, intraventricular heart-block disappeared. We have been unable to find in the literature the record of such an occurrence. It is for this reason that we wish to make report of this observation.

Although the rôle of sugar in the metabolism of cardiac muscle has been the subject of many investigations, the effect of the injection of glucose in abnormal cardiac rhythms such as occur in the clinic and may be recorded electrocardiographically has not been studied. That there is consumption of dextrose in the circulating fluid by the isolated and perfused mammalian heart was first shown by Johannes Müller[3]; the steps in the process of its utilization, however, are not at present definitely known.

CASE HISTORY

The patient, a male seventeen years old, was admitted to the hospital on November 29, 1928, complaining of weakness, dyspnea and swelling of the ankles. The patient was examined for life insurance five months previously and was told that albumin and red blood cells were present in the urine. He felt well, however, and continued working for one month when swelling of the ankles was observed. After four and one-half weeks in the hospital he became free of edema. One week later edema of the feet recurred. One month later he entered another hospital, having

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been free of symptoms although edema was still present. Here a diet high in protein content was given for one month. While in the second hospital and three weeks before admission to this hospital, he was suddenly seized with a chill and fainted. After this experience, he suffered from frequent attacks of fainting. He was occasionally nauseated and was short of breath for one month before admission to this hospital.

The patient's general health had always been good. He had an attack of measles during childhood from which he made a prompt recovery. He had suffered from colds and sore throats infrequently. Tonsillectomy had been performed twelve years before and a submucous resection of the nasal septum seven months before admission to hospital. There had been no cardiorespiratory, gastrointestinal or genitourinary symptoms until the onset of the present illness. His family history was unimportant.

On physical examination, the patient was a well-developed boy of seventeen years. There was pallor of the skin and mucous membranes. The pupils were regular and equal; they reacted to light and in accommodation. The fundi were normal on ophthalmoscopic examination. There was no tenderness over the sinuses. The ears were normal. The nasal septum was deflected to the right. The teeth and gums were in good condition. The tonsils appeared as small nodules buried in scar tissue. The breath was foul. The neck was normal. The lungs were normal to percussion and auscultation. The point of maximal impulse of the heart was felt in the fourth interspace, 6.5 cm. from the midsternal line. The rhythm was regular. A systolic murmur was heard along the left sternal margin. A diastolic murmur was not heard. The radial vessels were soft. The pulses were equal at the two wrists. The systolic blood pressure measured 166 mm. of mercury, the diastolic 86 mm. The abdomen was negative. The deep reflexes were present and active. There was pitting edema of the ankles.

On admission to hospital a twelve-hour concentrated specimen of urine contained 60,000,000 red blood cells, 10,000,000 white blood cells and epithelial cells, and 4,920,000 casts, 95 per cent of which were hyaline in type (Addis[4]).

The count of the red cells in the blood was 3,400,000 and that of the white cells 23,200, 84 per cent of which were polymorphonuclear, 10 per cent lymphocytes and 6 per cent transitionals. The oxygen capacity of the blood was 12.5 volumes per cent, equivalent to 68 per cent hemoglobin. The nonprotein nitrogen of the blood was 43 mg. per cent and the blood urea nitrogen 29 mg. per cent. The plasma proteins were reduced, the albumin to 1.6 per cent and the globulin to 2 per cent. The renal function as estimated by urea clearance was 27 per cent of normal (Möller, McIntosh and Van Slyke[5]).

In a two-meter x-ray photograph of the chest the heart did not appear to be enlarged.

The diagnosis according to the Addis classification[6] was hemorrhagic Bright's disease—active stage.

Course in Hospital

During the first five months the patient was under observation, the renal function, blood urea nitrogen, blood pressure and hemoglobin continued at the same level as on admission (Fig. 1). There was, however, a slight rise in the protein content of the blood plasma. During the fifth month tonsillectomy and adenoidectomy were performed to eliminate foci of infection. For several days after operation, oozing of blood from the nasopharynx occurred. Two weeks later the patient became anuric for three days. Catheterization at the end of that time yielded only 420 c.c. of urine. There were signs of uremia; vomiting started and became more frequent; the blood urea nitrogen rose to 114 mg. per cent (Fig. 1). Five days later, vomiting occurred several times each day; the patient became dehydrated and hypodermoclyses were given daily. On the morning of June 9,

1929, examination of the heart revealed the presence of gallop rhythm, best heard along the left border of the sternum. The rhythm was regular; a systolic murmur previously noted was still heard; the pulse was regular but weak. An electrocardiogram was taken immediately after examination. Intraventricular heart-block was present (Fig. 2, before injection of glucose intravenously). Since it had been observed on a previous occasion in another patient suffering from uremia, that which was thought clinically to be heart-block with syncope (Stokes-Adams syndrome) disappeared following the administration of hypertonic solution of glucose intravenously, 50 c.c. of a 50 per cent solution of glucose were given intravenously.

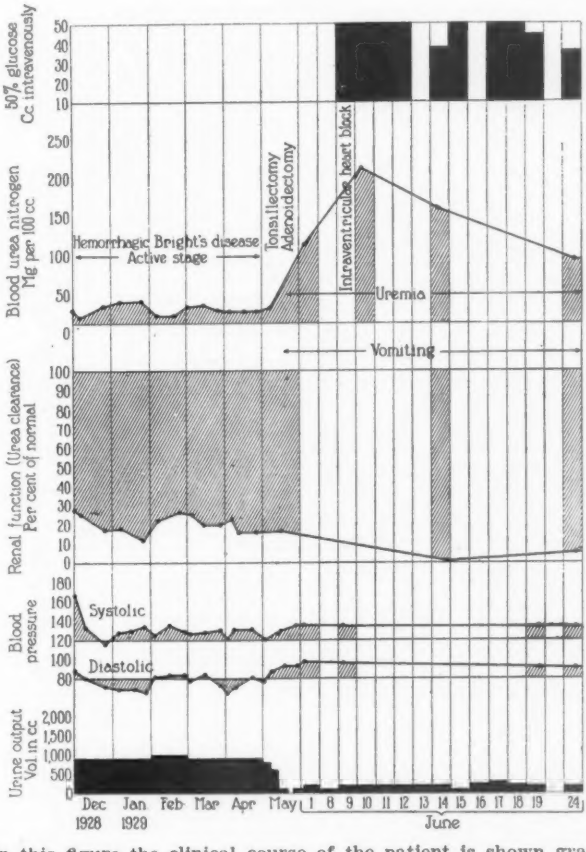

Fig. 1.—In this figure the clinical course of the patient is shown graphically. The output of urine, the blood pressure, the renal function and the blood urea nitrogen are recorded. Cross hatching indicates per cent deviation from normal, solid black represents amount in cubic centimeters. The day on which intraventricular heart-block occurred (June 9) is indicated.

There was an immediate change in the patient's condition as soon as the injection was begun: the gallop rhythm disappeared, the radial pulse became more forceful, and the patient volunteered the information that he felt very much better. Within one half hour a second electrocardiogram was taken; intraventricular heart-block had disappeared (Fig. 2, see description of electrocardiograms). Improvement was, however, temporary; the patient became drowsy and vomiting set in a few hours later. Gallop rhythm, however, did not recur, nor did intraventricular heart-block.

The next day, the blood urea nitrogen was 216 mg. per cent. Hypertonic glucose

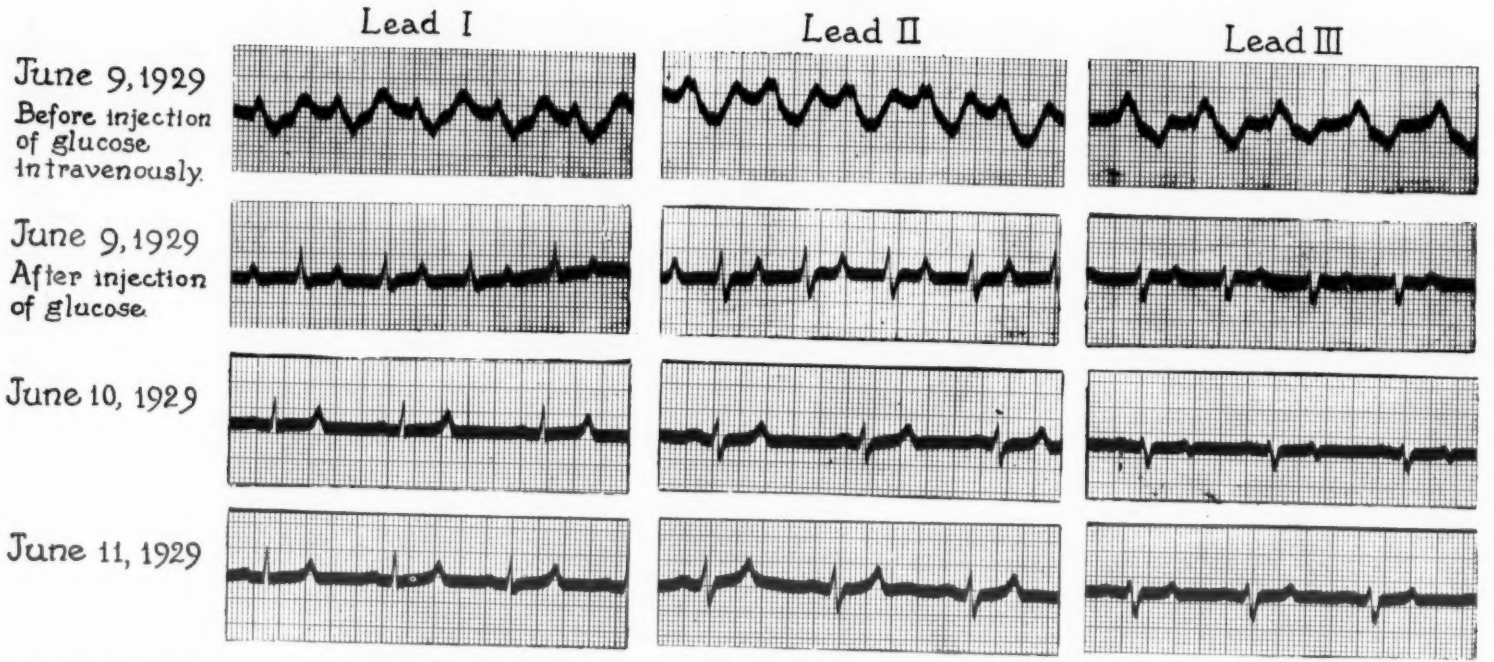

Fig. 2.—In this figure are presented the electrocardiograms derived from the patient. For description see text. The three standard leads of the electrocardiogram are shown. The standardization was such that a deflection of 1 cm. of the string was equivalent to 1 millivolt. Divisions of the ordinates equal 10-4 volts. Divisions of the abscissae equal 0.04 of a second. The electrocardiograms are reduced to five eighths of their natural size.

solution was administered daily on the next three days (Fig. 1). Temporary improvement occurred after each injection. Vomiting continued, however. A test of renal function made five days after the first injection of glucose showed that it was only 2 per cent of normal; blood urea nitrogen was 165 mg. per cent. During the next week glucose was given on five days, followed by a period of four days on which none was given. On June 24, the last day the patient was given glucose, the blood urea nitrogen was 96 mg. per cent; there was slight rise in renal function (Fig. 1), and the clinical symptoms of uremia were less marked. The patient gradually became worse, however, and died nine days later. Before death occurred the blood urea nitrogen increased to 127 mg. per cent and the urea clearance fell to 1.7 per cent of normal.

Electrocardiograms

The electrocardiograms taken immediately before injection of 50 c.c. of 50 per cent solution of glucose showed auriculoventricular rhythm (best seen in Lead III, Fig. 2). The prolonged QRS interval (0.16 of a second) together with splitting of the QRS waves gave indication of marked functional or anatomical alterations of the heart muscle. The slightly negative phase of the T-waves in Lead I was followed by a positive swing of greater voltage, while the deep negative phase of the T-waves in Leads II and III was followed by a positive swing. In short, *intraventricular heart-block was present.* The ventricular rate was 100 per minute. One half hour after the intravenous injection of glucose the electrocardiogram had changed; auriculoventricular rhythm was still present, the ventricular rate being 100 per minute. *Intraventricular heart-block was, however, no longer present.* The QRS time had decreased to the extent that it was now within normal limits. There was left axis deviation. It may be recalled that coincident with these changes the radial pulse improved in force, and there was marked subjective and objective improvement. The next day (June 10, twenty-four hours later) the rhythm was normal and the ventricular rate slower (70 per minute). The conduction time in Lead II was 0.16 to 0.17 of a second. The T-waves in Lead III were diphasic. There was still slight splitting of the QRS complexes, the QRS time, however, was within normal limits. The next day the rhythm remained normal and the P-R interval was 0.2 of a second. The only change to be observed in the form of the curves was that the T-waves in Lead III, which had been diphasic, were now upright and of greater voltage. From that time the electrocardiograms remained essentially unchanged. There was no recurrence of intraventricular heart-block.

DISCUSSION

The cause of the changes which occur in electrocardiograms in the course of uremia can be at present only a matter of conjecture. The abnormalities which have been found have been attributed to nitrogen retention. Wood and White[2] found, however, that no correlation existed between the degree of nitrogen retention and the tendency to exhibit electrocardiographic changes. From observations made on the electrocardiograms of patients, Robinson[7] has attributed transient intraventricular heart-block to a state of poor nutrition of heart muscle. That the changes are more likely to be of a toxic nature (functional changes) than due to anatomical lesions is clearly demonstrated in the case of our patient, by the rapidity of the disappearance of the abnormality. Several days before the onset of uremia there was anuria and associated with this a rise in blood urea nitrogen (from 35 mg.

per cent to a level of 216 mg. per cent). It was then, when the urea clearance was only 2.4 per cent of normal, that his electrocardiogram showed the presence of intraventricular heart-block. One-half hour after the injection of 50 c.c. of 50 per cent solution of glucose intravenously intraventricular heart-block disappeared, and the patient's general condition began to improve. Other observers (Budingen,[8] Isaac[9]) who have used hypertonic glucose solutions intravenously in a variety of conditions have observed an increase in force and volume of the radial pulse. This effect has been attributed by them to two factors: in the first place, to the improved nourishment of the heart muscle; and in the second place, to an osmotic pressure effect due to the fact that hypertonic glucose solutions draw water from edematous heart muscle. Their argument presupposes, of course, that there is edema of heart muscle.

A basis for the use of glucose solutions in states in which it is believed the muscle is undernourished is found in a long series of experiments. It may be recalled that Johannes Müller[3] first demonstrated that there is consumption of dextrose in the circulating fluid by the isolated and perfused mammalian heart; Stewart[10] made a similar observation in regard to the artificially perfused human heart. Locke and Rosenheim[11] showed that there is a definite relation between the amount of sugar consumed and the length of time during which the heart is kept beating. In perfusing hearts of rabbits Claes[12] demonstrated that the presence of an increased amount of glucose in the perfusion fluid is very favorable for the work of the heart and that the excitatory action of adrenalin is prolonged by it. The effect of cardiac rate on the utilization of sugar has also been studied. Patterson and Starling[13] found that an acceleration of the rate due to adrenalin causes increase in sugar consumption. And if insulin is added to the blood of the heart-lung preparation, Plattner[14] found that the rate of disappearance of blood sugar did not increase so long as the rate was not accelerated; if it did, the disappearance of sugar was found to increase in the same ratio after the addition of insulin to the perfusion fluid. Hepburn and Latchford[15] showed that the addition of insulin to the perfusion fluid accelerated the removal of dextrose therefrom by the isolated mammalian heart. Burn and Dale[16] have shown that the extra sugar does not disappear by combustion.

The energy requirements of the heart for a given stroke volume increase with an increase in the diastolic volume, so that the efficiency decreases (Starling and Visscher[17]). In the heart-lung preparation the heart slowly and continually dilates; although, according to Starling, under physiological conditions it always works at the smallest possible volume and with a maximum efficiency; this dilatation can be abolished by the addition of insulin (Visscher and Müller[18]). Bayliss, Müller and Starling[19] have shown that the heart volume can be re-

duced by the addition of insulin to the perfusate, but the effect is transitory unless glucose is also given either before or after insulin, when it lasts an hour or more. Neither insulin nor sugar has any action on hearts already working efficiently. The volume of the heart is reduced by adding glucose alone as well as insulin alone, and by the same terms its efficiency is increased. In the absence of insulin enormous concentrations of glucose are needed in the blood in order to permit the heart to function properly, and subsequent addition of insulin causes a rapid disappearance of much of this glucose. The sugar does not, as has already been suggested, disappear by combustion. The results are explained by assuming a reaction between free glucose and a substance which they call "stored glucose" or "glucose complex," in the elaboration of which insulin plays a part. Edmunds and Cooper[20] have observed in dogs a rise in blood pressure following the intravenous injection of glucose in the circulatory failure which follows the injection of diphtheria toxin.

It appears then both from experiments in the laboratory and from observations made in the clinic that glucose has an influence upon the behavior of cardiac muscle. The effect may be stated in a general way to favor the mechanical capability of the muscle. From our experience in this case it appears that glucose has a further influence, for as a result of giving it the propagation of the excitatory wave through the ventricular muscle was improved. The muscle cells, in which before there was a delay in the propagation of the excitatory process, were altered in such a fashion that the excitatory wave now passed through the muscle in a time which was within normal limits.

It is not possible to state accurately by what mechanism the injection of glucose induced the changes in the electrocardiograms which were observed; whether by improved nutrition of the heart muscle or by an osmotic pressure effect, by a combination of the two, or by some other factors. That there was an association between the occurrence of intraventricular heart-block in uremia and its disappearance in this patient following the injection of glucose is apparent.

SUMMARY

Report has been made of the disappearance of intraventricular heart-block occurring in the course of uremia following the intravenous injection of hypertonic solution of glucose.

REFERENCES

1. Heitz, Jean: Sur l'azotémie des sujets présentant le pouls alternant, Progrès méd. **36**: 67, 1921.
2. Wood, J. E., and White, P. D.: The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention, Am. J. M. Sc. **169**: 76, 1925.
3. Müller, J.: Studien über die Quelle der Muskelkraft. I Mitteilung über den Zuckerverbrauch bei der Muskelarbeit, Ztschr. f. allg. Physiol. **3**: 282, 1904.

4. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, J. Clin. Investigation **2**: 409, 1926.
5. Möller, E., McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion. IV. Relationship Between Urine Volume and the Rate of Urea Excretion by Patients with Bright's Disease, J. Clin. Investigation **6**: 485, 1928.
6. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85**: 163, 1925.
7. Robinson, G. C.: The Relation of the Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, Arch. Int. Med. **18**: 830, 1916.
8. Budingen, T.: Stoffwechselbehandlung des Herzens (Kardiotrophototherapie) mittelst Einläufen hypertonischer Traubenzuckerlösungen in die Blutbahn, Schweiz. med. Wchnschr. **4**: 395, 1923.
9. Isaac, S.: Ueber Beeintlussung der Herztätigkeit und der Diurese durch intravenöse Traubenzuckerinfusionen, Therapeutische Halbmonatshefts **35**: 698, 1921.
10. Stewart, H. A.: The Dextrose Consumption by the Isolated Perfused Human Heart, J. Exper. Med. **12**: 59, 1910.
11. Locke, F. S., and Rosenheim, O.: Contributions to the Physiology of the Isolated Heart. The Consumption of Dextrose by Mammalian Cardiac Muscle, J. Physiol. **36**: 205, 1907-08.
12. Claes, E.: Influence du glucose sur les effets de l'adrénaline sur le coeur isolé du lapin. Compt. rend. Soc. de biol. **2**: 783, 1922.
13. Patterson, S. W., and Starling, E. H.: The Carbohydrate Metabolism of the Isolated Heart-Lung Preparation, J. Physiol. **47**: 137, 1913-14.
14. Plattner, F.: The Influence of Insulin on the Blood Sugar in the Heart-Lung Preparation, J. Physiol. **59**: 288, 1924-25.
15. Hepburn, J., and Latchford, J. K.: Effect of Insulin (Pancreatic Extract) on the Sugar Consumption of the Isolated Surviving Rabbit Heart, Am. J. Physiol. **62**: 177, 1922.
16. Burn, J. H., and Dale, H. H.: On the Location and Nature of the Action of Insulin, J. Physiol. **59**: 164, 1924-25.
17. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, J. Physiol. **62**: 243, 1926-27.
18. Visscher, M. B., and Müller, E. A.: The Influence of Insulin Upon the Mammalian Heart, J. Physiol. **62**: 341, 1926-27.
19. Bayliss, L. E., Müller, E. A., and Starling, E. H.: The Action of Insulin and Sugar on the Respiratory Quotient and Metabolism of the Heart-Lung Preparation, J. Physiol. **65**: 33, 1928.
20. Edmunds, C. W., and Cooper, R. G.: The Action of Cardiac Stimulants in Circulatory Failure Due to Diphtheria, Tr. A. Am. Physicians **60**: 54, 1925.

PAROXYSMAL TACHYCARDIA WITH MYOCARDIAL LESIONS*

A Case Report

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MANY observations have been made upon paroxysmal tachycardia in the past few years, but most of these studies deal largely or entirely with electrocardiographic aspects of this condition. The number of cases in which pathological studies have been reported is comparatively small.

In 1926 we[1] reported a case of paroxysmal tachycardia, probably of ventricular origin, in which the heart showed numerous foci of myocarditis, obviously the result of infection. We have recently had the opportunity of studying a patient suffering from paroxysmal tachycardia of auricular origin, who died during the attack and on whom a necropsy was obtained. The history of this patient is as follows:

Mrs. G. N., aged thirty-four years, was admitted to the Bell Memorial Hospital complaining of rapid heart, nausea, and swelling of the abdomen.

Family History: Essentially negative.

Past History: The patient was married and had three children. There is no history of miscarriages or difficulty in labors. The patient has had attacks of rapid beating of the heart, coming on suddenly and disappearing equally suddenly three or four time a year since she was thirteen years old. The duration of these attacks has varied from a few minutes to two days. During the past six months, she has had two attacks, each of which lasted only one hour. The patient has suffered for years from numerous attacks of tonsillitis and her tonsils were removed one year ago and found to be badly infected.

Present Illness: The present illness began suddenly two weeks before admission to the hospital. This attack resembled the previous attacks the patient had had, but has continued much longer than any previous attack. The past few days the patient has been blue and very short of breath.

On physical examination the patient had a strikingly distressed and anxious look, the precordium was heaving and it was obvious that the heart was beating at a rapid rate. The pulse was so rapid that it could not be counted at the wrist. The patient's blood pressure was 90 mm. systolic and 60 mm. diastolic; respiration was rapid (40 per minute); and on auscultation there were numerous fine, moist râles heard throughout the chest.

The liver was palpable 6 cm. below the costal margin in the right mammillary line; the abdomen was distended, and there was a marked fluid wave. Both legs were edematous and pitted on pressure. The urine showed a trace of albumin, the blood examination showed: R.B.C. 4,000,000; W.B.C. 14,200; hemoglobin 70 per cent. The roentgenographic findings showed an increase in the size of the heart and evidences of chronic pulmonary tuberculosis at a hilum of the lung. The electrocardiograph showed the heart rate to be 240 per minute.

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The clinical picture was that of a paroxysmal tachycardia which had continued such a length of time as to produce a marked myocardial insufficiency. The electrocardiogram taken of this patient (Fig. 1) shows a tachycardia, probably of auricular origin. The patient was given strophanthin intravenously, combined with luminal and morphine, and she also received several doses of quinidine. Following the use of quinidine, there seemed to be a progressive slowing in the heart rate, and on December 31 the pulse rate was diminished to 180; on January 1 the pulse rate was down to 164; on January 3 the pulse rate was 160; on January 4 in the

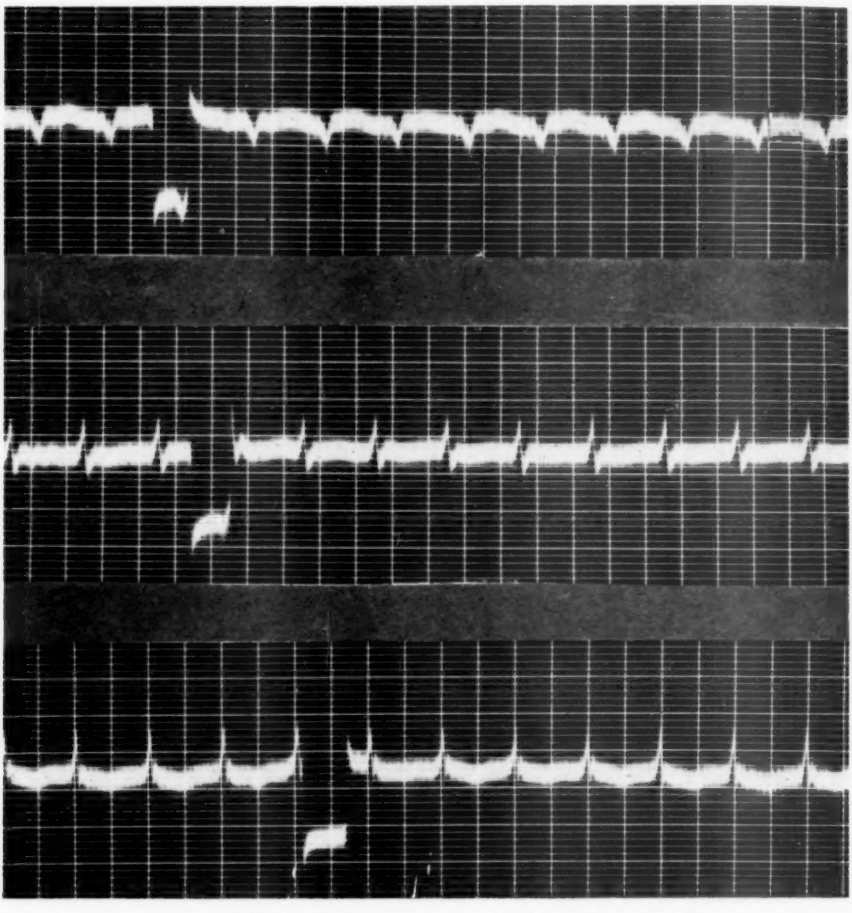

Fig. 1.—Electrocardiogram of heart during tachycardia.

morning, the rate was 148, falling to 100 in the afternoon. The morning of January 5 the pulse rate again rose to 151 and, shortly after, the patient became very cyanotic and died suddenly. A few minutes before death she seemed apparently comfortable, smiled, talked, and expressed herself as feeling very much better.

Autopsy: The autopsy was performed the same day. The anatomical diagnosis was: acute and chronic myocarditis (focal); acute mural endocarditis with organizing mural thrombosis; chronic pericarditis with subepicardial hemorrhages; fragmentation and segmentation of the myocardium; hypertrophy and dilatation of the heart; infarction of the lungs; pulmonary thrombosis; general anasarca;

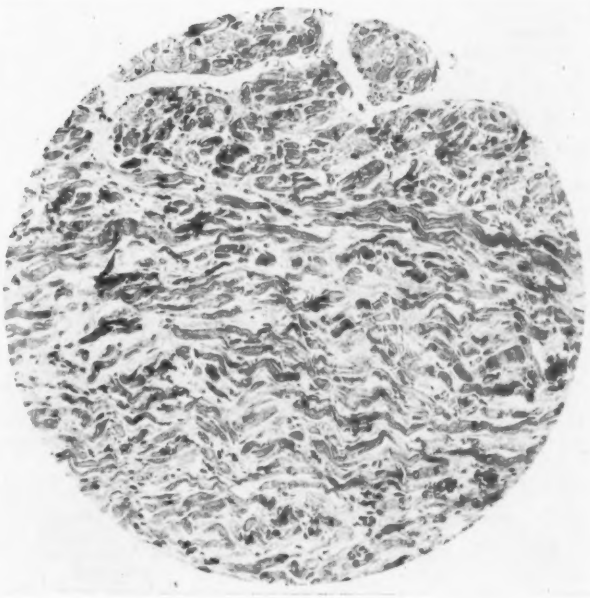

Fig. 2.—Section of myocardium in ventricle showing fibrosis, fragmentation, and necrosis of muscle cells. (Magnification ×200.)

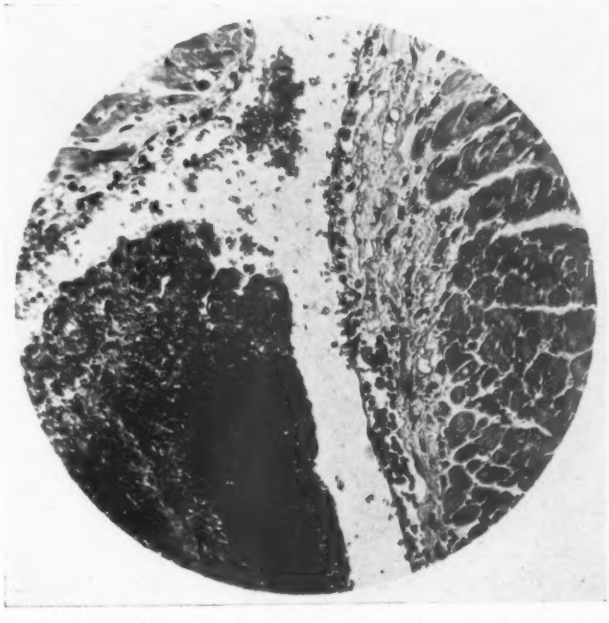

Fig. 3.—Mural endocarditis showing edge of thrombus. (Magnification ×175.)

toxic nephrosis; acute and chronic pancreatitis; chronic passive congestion of the liver, lungs, and kidneys; fatty degeneration of the kidneys; partly healed caseous tubercle of the lungs; chronic adhesive pleurisy; atelectasis, chronic bronchitis, and chronic pneumonitis.

The most interesting necropsy findings were in the heart. The pericardial sac was distended with fluid. The surfaces were smooth, moist, and glistening. The heart weighed 345 grams and measured 12 by 10 by 8 cm. and was normal in shape. It was firm, reddish-brown, somewhat dilated, and the chambers were filled with fluid blood. The foramen ovale was closed. The pericardial surfaces were smooth, moist, and glistening. Thrombotic masses were adherent to the auricular wall, particularly on the right side, but elsewhere the mural and valvular endocardium was normal. The subepicardial fat was scanty, but in the auricles it showed a number of small petechial hemorrhages. The myocardium of the right ventricle

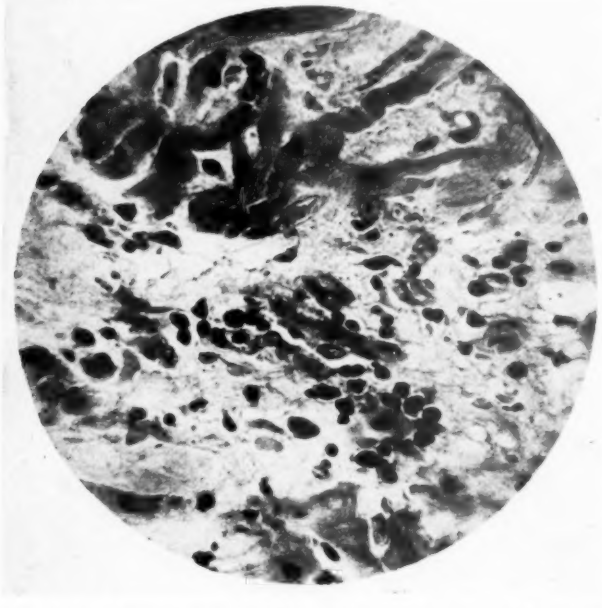

Fig. 4.—Perivascular inflammatory reaction in myocardium. (Magnification ×400.)

varied from 4 to 7 mm. in thickness and that of the left, from 16 to 20 mm. The chordae tendineae and papillary muscles showed nothing abnormal. The circumferences of the valve rings were as follows: tricuspid 13, mitral 11, pulmonary 8.5, and aortic 6 cm. The coronary arteries showed nothing abnormal.

On microscopic examination the pericardium was thickened. It showed here and there foci of lymphoid cells, especially about some of the blood vessels. In some places there was congestion of the vessels associated with focal hemorrhages and lymphoid cell infiltration. The changes in the pericardium and in the musculature of the auricles were more striking than those in the ventricles. The endocardium was in places slightly thickened, and showed some infiltration of leucocytes. One area showed both polynuclear and mononuclear leucocytes extending throughout the endocardium, and adjacent to this was a typical early organizing thrombus. The endocardial lesions here also were limited to the auricles. The muscle fibers of the auricles showed marked atrophy with degeneration and some replacement by fibrous

tissue. In some microscopic fields there was much fragmentation and segmentation and necrosis. The cross striations of the muscle fibers were often obscure; and many fibers showed marked vacuolar and granular degeneration with pyknotic, irregular, and hyperchromatic nuclei. In some foci the stroma was considerably increased in amount, particularly in the neighborhood of the blood vessels. Foci of leucocytes were fairly common, which showed large mononuclear cells, often with eosinophilic cytoplasm. Occasionally polynuclear leucocytes were seen, usually in some of the congested blood vessels. Although these degenerative changes were also seen in the ventricle, most of the focal inflammatory changes were seen in the auricle.

A section of the heart muscle stained with scharlach R showed some fat droplets in the muscle fibers, particularly near the nuclei. Some of these droplets were lipochromes.

The degenerative and inflammatory foci were more marked and numerous in the auricle than in the ventricle. The inflammatory changes were not only acute but also chronic, there being rather extensive diffuse fibrosis particularly in the sections of the auricle.

This patient who suffered from paroxysmal tachycardia showed at autopsy an acute and chronic myocarditis. This myocarditis was very obviously infectious, and the patient's infected tonsils, which were removed approximately one year before the onset of this attack, may have been the portal of entry for the infection.

It is interesting that this patient's attacks at first had a very sudden onset and a sudden termination, and clinically belonged definitely in the group described by Bouveret, who insisted upon this criterion for diagnosis. In this last attack, however, the tachycardia did not cease suddenly, but gradually, the patient's pulse coming down to normal over a period of four days. The duration of this attack was unusually long, the patient having had the condition two weeks before admission and being under observation ten days in the hospital—twenty-four days in all.

REFERENCE

1. Major, Ralph H., and Wahl, H. R.: Paroxysmal Tachycardia Associated With Focal Myocarditis, J. A. M. A. 86: 1125, 1926.

SO-CALLED INTERPOLATION OF EXTRASYSTOLES DURING IDIO-VENTRICULAR RHYTHM*

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THE term interpolation in clinical electrocardiography is used to denote interposition in a series. An interpolated ventricular extrasystole is interposed between two beats of the sequence initiated from the pacemaker. It differs in effect from the ordinary ventricular extrasystole in that it fails to block completely, although it may delay the transmission of the next expected beat of the sequence.

Interpolation occurs readily when the combination of slow heart rate and highly premature beats is present. These circumstances permit time for recovery of the junctional tissues after block of the retrograde impulse of the premature beat before the next expected impulse from the pacemaker arrives. If, however, idio-ventricular rhythm is present the state of affairs becomes very unfavorable for interpolation because of the comparative accessibility of the pacemaker to the influence of the excitatory wave of the premature beat. Nevertheless, interpolation is theoretically possible and should occur if the idio-ventricular pacemaker is protected from the premature beat and the conducting tissues between the pacemaker and the ventricles recover rapidly enough to transmit the next expected excitatory wave.

Weiser[1] has reported a case of transient complete heart-block due to digitalis, in which ventricular extrasystoles caused only very slight disturbance in the fundamental idio-ventricular rhythm. He interpreted his curves as showing interpolation of ventricular extrasystoles and referred to tracings previously published by Fahrenkamp[2] and Singer and Winterberg[3] which he believed also exhibited interpolation. Singer and Winterberg's tracing is susceptible of an entirely different interpretation which need not be considered here. A characteristic of Fahrenkamp's as well as Weiser's curves was the fact that the cycles containing extrasystoles were slightly longer than uninterrupted cycles. This finding is somewhat difficult to harmonize with the interpretation given, but Weiser assumed that it was due to temporary delay in responsiveness of ventricular muscle to excitation caused by incomplete recovery from the preceding extrasystole. Although Weiser does not so state, the delay in his case would have to occur in the auriculo-ventricular bundle because of similarity of ventricular complexes. However, if the disturbance involved the rate of trans-

*From the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

mission rather than the rhythmic discharge, one would expect the delay in the cycle containing the extrasystole to be compensated for in the next succeeding cycle or cycles. This evidence would be necessary in Weiser's case to establish clearly his contention that the extrasystoles are actually interpolated and not due to interference with the centre. Unfortunately, the tracings do not furnish this data but it is stated that cycles containing extrasystoles have a duration of 1.55 second and other cycles 1.50 second.

We have obtained tracings in one case of complete heart-block with ventricular extrasystoles in which the cycle containing extrasystoles are 0.06 to 0.07 second longer than other cycles, (Figure 1) a time relation practically identical with that of Weiser's case. In our case the delay was not compensated for in the succeeding cycle. It is therefore necessary to conclude that the extrasystoles caused a disturbance in the rhythmic discharge of excitations rather than in their transmission.

If one speculates as to the mechanism concerned in our case, two possibilities present themselves. First, the premature excitation of an extrasystole may reach the active idio-ventricular centre and abolish the impulse building there but fail to reach another centre capable of discharging impulses at a slightly slower rate. Thus, after an extrasystole, such a centre which had been protected from the premature disturbance would be given an opportunity to discharge an excitation. In both Weiser's and Fahrenkamp's cases this view finds support in that the presence of slight changes in the QRS complexes following extrasystoles suggest that the excitation had spread through a slightly different pathway. This finding is especially noteworthy in Fahrenkamp's case which showed a succession of cycles, each containing what Weiser interpreted as an interpolated extrasystole. Alternate differences in QRS complexes were present as though two idio-ventricular centres were alternating in activity. McMillan and I[4] have pointed out the possibility that differences in ventricular complexes may depend upon differences in the lengths of pathways to the main branches of the bundle. Thus a centre just above the bifurcation nearer the right main branch might be expected to excite responses with ventricular complexes slightly different from those of a centre nearer the left main branch.

The second possibility assumes that the regularly functioning idio-ventricular centre is actually protected from the premature impulse but that the extrasystole causes a reflex nervous disturbance which acts on the centre, delaying the discharge of the next expected excitation. This assumption finds support in the fact that an extrasystole not infrequently disturbs the next few beats of sinus rhythm; an effect doubtless due to reflex nervous influence. Furthermore, there is excel-

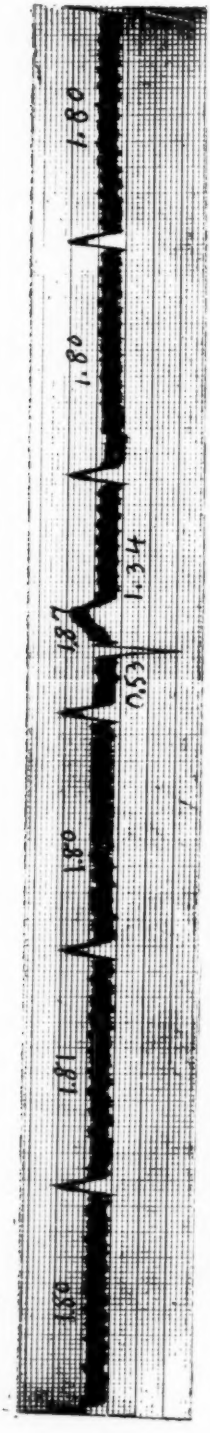

Fig. 1.—Auricular fibrillation and complete heart-block. The ventricular rhythm was remarkably constant except that cycles containing extrasystoles were 0.06-0.07 second longer than others. Exertion and atropin (gr. 1/100 hypodermically) had no effect on the idio-ventricular rate. Tracing made three weeks later was identical except that no extrasystoles were recorded.

lent evidence that both the vagus and sympathetic nerves are sometimes capable of exerting effects on idio-ventricular centers below the point of complete block.[5]

Neither of the above proposed mechanisms, strictly speaking, would justify designating the extrasystoles as interpolated. The term should not be applied in the present state of our knowledge, to extrasystoles during idio-ventricular rhythm unless the dominant rhythm were to remain undisturbed or evidence could be furnished that delay in the beat after an extrasystole is due to prolongation of conduction time from the pacemaker to the ventricles.

The clinical significance of these unusually short pauses after extrasystoles does not depend on whether or not the extrasystoles are interpolated but on the fact that the short pauses may occur during complete heart-block. Their presence therefore should not lead to an erroneous diagnosis of incomplete block.

SUMMARY

An electrocardiogram obtained from a patient with complete heart-block and what might be regarded as interpolated extrasystoles is presented. The mechanism and the possibility of this being true interpolation are discussed.

It is concluded that, thus far, there has been no proof of the occurrence of interpolated beats during idio-ventricular rhythm.

REFERENCES

1. Weiser, E.: Deutsches Arch. f. klin. Med. **140**: 73, 1922.
2. Fahrenkamp, K.: Deutsches Arch. f. klin. Med. **120**: 35, 1916.
3. Singer, R. and Winterberg, H.: Wiener Arch. f. inn. Med. **1**: 394, 1920.
4. Wolferth, C. C. and McMillan, T. M.: AM. HEART J. **4**: 521, 1929.
5. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat. 3rd Ed., page 423. London 1925.

COMPLETE HEART-BLOCK ASSOCIATED WITH RAPID VENTRICULAR RATE. REPORT OF TWO CASES*

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COMPLETE heart-block is usually associated with ventricular bradycardia. We have recently observed two cases of complete A-V dissociation in which the ventricular rates were rapid, approximately 90 per minute. The association of relative ventricular tachycardia with complete heart-block in cases of auricular sinus rhythm is rare. Lewis[1] makes no mention of it, although he does discuss rapid ventricular rates with complete block in cases of auricular fibrillation. In a review of the literature we have found only six cases resembling the two we are reporting. Luten[2] records four cases of complete A-V dissociation with ventricular rates over 90 in patients who were getting massive doses of digitalis. Carr and Reddick[3] report two cases, one with a ventricular rate of 71 occurring during the acute stage of rheumatic fever in a patient who received 30 c.c. of the tincture of digitalis, and another with a ventricular rate of 83 in a patient who did not receive any digitalis. Dr. William A. Brams has been kind enough to show us an electrocardiographic tracing of a case similar to ours but whose clinical record is unknown. A number of instances are recorded in which the rapid ventricular rate occurring in complete heart-block resulted from ectopic ventricular beats or from two coexisting alternating foci in the ventricles, but the seven cases mentioned and our two are the only ones we can find in which the hyperirritability of the ventricles is manifested by the existence of a single ventricular focus. This focus in each of our cases appears to have been located in or near the A-V node.

REPORT OF CASES

CASE 1.—L. R., male, aged fifty-five years, was admitted to the medical service of Dr. Walter W. Hamburger on February 25, 1929, because of cough, expectoration, dyspnea and edema which had progressively increased over a period of four months. For three months he had been complaining of some left-sided chest pain. Some dyspnea had been present on exertion for the previous two years. The past history was negative except for a cystotomy three years previously for a vesical calculus.

At the time of admission the patient appeared acutely ill; was orthopneic, moderately cyanotic, respirations were Cheyne-Stokes in character, and there was a distinct uriniferous odor to the breath. The mentality was not clear, and the speech was rambling in character. The heart on percussion was enlarged to the left

*From the Medical Services of the Michael Reese Hospital, Chicago.

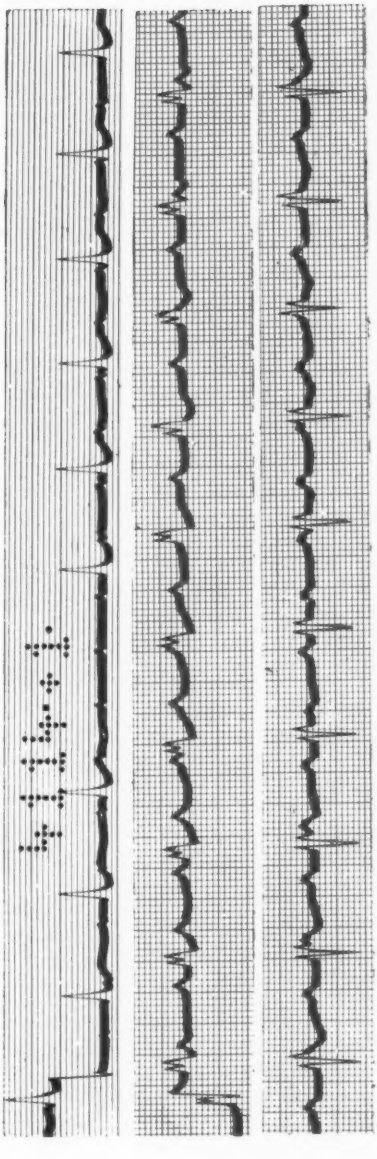

Fig. 1.—Case 1. March 5, 1929. Complete A-V dissociation. The ventricles are responding to a focus in the bundle of His at a rate which varies from 83 to 88 per minute. The auricular rate is approximately 150 per minute. In Lead I, the fourth ventricular cycle is followed by a complete dropping out of the expected ventricular complex. Left axis deviation.

and right, the borders measuring 11 cm. and 4.5 cm. respectively. The rate was rapid. No murmurs were heard. Marked arteriosclerosis was present. Signs of considerable fluid in the right pleural cavity were present, and there were numerous coarse râles in the lower left lung. The liver was enlarged and tender, extending three fingerbreadths below the costal margin. Dullness in the flanks and a fluid wave were elicited in the abdomen. There was marked edema of the legs. The temperature on admission was 100° F., pulse 96, respirations 24. The white blood count was 10,500 with 72 per cent polymorphonuclear cells. The urine contained ++ albumin but no cells or casts. Blood pressure was 144/90 mm. The Wassermann test was negative. The diagnosis on admission included arteriosclerotic heart disease with congestive failure, arteriosclerotic nephritis and uremia.

On February 27, the nonprotein nitrogen of the blood was 62 and creatinin 1.6 mg. per 100 c.c. of blood. Tincture of digitalis, ℥ xxx 4 times daily, was ordered. The general condition remained about the same for three days, following which

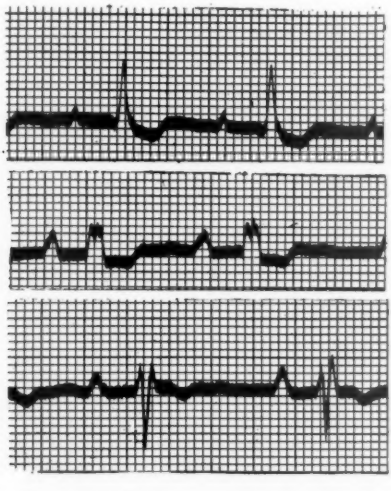

Fig. 2.—Case 1. March 12, 1929. Return to sinus rhythm. P-R interval varies from 0.2 to 0.24 second. The prolongation of the P-R interval is probably due to residual effects of digitalis. Evidences of generalized myocardial damage are present. Left axis deviation.

there was gradual disappearance of the fluid. By March 3, the patient felt greatly improved. Digitalis was continued in the same dosage until March 6 when the patient vomited. This was the first sign of overdigitalization. Digitalis was stopped. The following day the electrocardiogram, which had been taken on March 5, was returned revealing a complete heart-block with a relatively rapid ventricular rate (Fig. 1). On March 12, another electrocardiogram showed that the A-V dissociation had disappeared but that the P-R interval was increased from 0.2 to 0.24 second (Fig. 2). On March 28, the P-R interval had diminished to 0.16 second. On March 18, the nonprotein nitrogen was 39 and creatinin 1.3. Aside from an attack of what was thought to be a right-sided renal colic, the rest of the patient's stay at the hospital was uneventful, and he was discharged March 30 without digitalis. When last seen, April 20, 1929, he was slightly dyspneic. The heart rate was 96. There were no murmurs heard. The lungs were clear, the liver was detected one fingerbreadth below the costal margin, and there was slight edema of the legs.

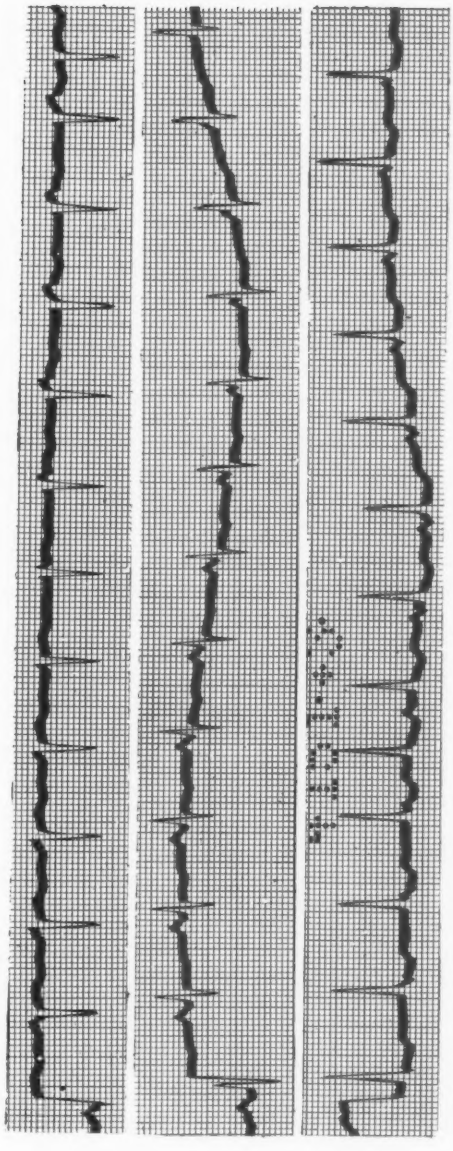

Fig. 3.—Case 2. March 19, 1929. Complete A-V dissociation. The ventricular focus lies in the bundle of His and has a rate of 96 per minute. In Lead III there are two ventricular cycles equal to each other but having a duration which corresponds to a rate of 130 per minute. Right axis deviation.

CASE 2.—Mrs. J. M., a forty-four-year-old widow, a silk worker, was admitted to the medical service of Dr. Sidney Strauss, March 15, 1929, complaining of dyspnea on exertion and weakness of four years' duration, cough, orthopnea and pain in the chest for two weeks. She gave a history of heart trouble for fifteen years, but no rheumatic attacks were known. For one day before admission she was taking tincture of digitalis, ℥ xv three times daily, and for four days before that she was taking some brownish bitter medicine, the character of which we were unable to determine, in teaspoonful doses three times daily. The patient stated that this was given for her heart.

Examination showed an emaciated woman of about forty-five years who was very dyspneic and was coughing. Temperature 100° F., pulse 96 and regular, respirations 24, and blood pressure 150/115 mm. Râles were heard at both bases.

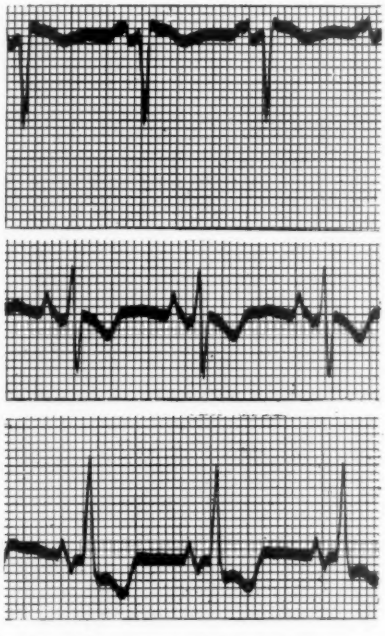

Fig. 4.—Case 2. March 26, 1929. Sinus rhythm with rate of 68. P-R interval 0.16 second. P-wave is notched in Leads I and II and diphasic in III. T-wave is inverted in all leads and is typical of digitalis intoxication. Right axis deviation.

Heart was enlarged, and there was a rough presystolic murmur and a soft systolic murmur at the apex with reduplication of the second tone throughout. There were no irregularities. The liver was down 8 cm., and there was edema of the legs. The diagnosis made was rheumatic heart disease with a double mitral lesion and heart failure, and possible recurrent endocarditis to account for the slight fever. The next day she began to have pain in the left knee, and a diagnosis of arthritis was made. The fever continued for several days. The white blood count on admission was 16,200. Urine showed ++ albumin.

Blood chemistry was normal. The Wassermann test was negative.

The patient was given tincture of digitalis, ℥ xx three times daily. On March 17 the patient showed frequent extrasystoles, but the pulse rate was 100. Digitalis was continued. On March 19, four days after admission, an electrocardiogram showed complete A-V dissociation with regular ventricular rate of 96 and an

auricular rate of 94-100 (Fig. 3). Digitalis was stopped March 23, 1929. The rate then was 84 and regular. The heart findings were the same, and the general condition was improving. On March 26, three days after stopping digitalis, the electrocardiogram showed sinus rhythm with a rate of 88 and a P-R interval of 0.16 second (Fig. 4).

DISCUSSION

It is well known that in cases of auricular fibrillation when complete heart-block supervenes (as, for example, in digitalization) bradycardia usually is present, but not infrequently relatively rapid ventricular rates may occur. The possibility that similar ventricular tachycardia may occur in cases where auricular sinus rhythm exists seems to have received little attention. Luten believes that in his four cases digitalis was responsible for the changes in conduction, and in our first case we feel reasonably certain that the large dosage of digitalis produced the complete block with the hyperirritability of the ventricles. In our second case, like one of those reported by Carr and Reddick, it seems possible that a combination of toxins—digitalis and a toxin of the rheumatic infection—produced the changes.

It is generally recognized that digitalis can produce complete heart-block, but the mechanism of its production is not clear.[4] Luten[2] in studies on cats has pictured the sequence of events in digitalis poisoning as follows: (a) inversion of the T-wave, (b) depression of A-V conduction and slowing of the heart rate, (c) acceleration of the auricles and ventricles, (d) complete A-V dissociation with a ventricular rate higher than that of the auricles, (e) abnormal ventricular rhythms, (f) ventricular fibrillation and death. Crawford[5] says that "in the advanced stages of digitalis poisoning it is known that ventricular extrasystoles appear and that ventricular tachycardia may supervene. This is due to a direct action of digitalis on the heart muscle which may cause a focus in the ventricle to give out impulses at a greater rate than the normal pacemaker, so that the former controls the ventricular rate." In our two cases, two phenomena are evident—complete A-V dissociation resulting from depression of A-V conduction, and hyperirritability of the ventricles with the development of a single focus in or near the A-V node.

We have mentioned two factors which may be responsible for the production of the changes in the heart activity described, i.e., digitalis and the existence of an acute infection. Another possible factor in our first case was the uremia, the patient having been in partial uremia for several days, although at the time the electrocardiogram was taken the uremic manifestations had disappeared. Mohler[6] in a recent article has called attention to the interesting association of uremia and heart-block, recording a case in which the A-V dissociation appeared during

uremia, disappeared with clearing of the uremia, and returned with the recurrence of the uremic state. In this case the ventricular rate was 30.

In recording these two cases, we wish particularly to point out that the presence of complete heart-block may be completely masked clinically by the existence of a relative ventricular tachycardia. In neither case reported was bradycardia present, and the rhythm was always regular except in the second case where the development of complete heart-block was preceded by numerous extrasystoles. There was nothing beyond the electrocardiograms to suggest heart-block.

We wish to thank Drs. W. W. Hamburger, Sidney Strauss, and W. A. Brams for their kind help in the preparation of this paper.

REFERENCES

1. Lewis, Sir Thomas: The Mechanism and Graphic Registration of the Heart Beat, 1925, Paul B. Hoeber.
2. Luten, Drew: Clinical Studies of Digitalis, Arch. Int. Med. 35: 74, 1925.
3. Carr, J. G., and Reddick, W. G.: Conduction Disturbances in Acute Rheumatic Infections, J. A. M. A. 91: 853, 1928.
4. Robinson, G. C.: Therapeutic Use of Digitalis, Medicine 1: 1, 1922.
5. Crawford, J. H.: Observations on a Case of Heart-Block in Acute Rheumatic Fever Under Treatment With Digitalis, Am. Heart J. 3: 196, 1927.
6. Mohler, H. K.: Heart Block and Uremia, J. A. M. A. 92: 706, 1929.

STANDSTILL OF THE HEART OF VAGAL ORIGIN

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INSTANCES of standstill of the heart due to vagal inhibition are rare. The case to be reported is of interest as an example of this condition. Moreover, the immediate cause of the excessive vagal tone responsible for bradycardia and standstill in this patient is believed to be primarily psychic.

CASE REPORT

History.—The patient, a young man of twenty-two years, came to this clinic on June 16, 1928. Save for the fact that his father had died of pulmonary tuberculosis, the family history was negative. The boy's mother was sure he was not a "blue baby." During early life the child was sickly, but save for a severe attack of whooping cough he had no serious illness. He had frequent attacks of tonsillitis. As a child he was difficult. He did not do well at school and could not get along with the other boys. Only during the past two years had he become more sociable. While attending a private school at sixteen years of age he had an acute attack of illness which began with vomiting and diarrhea. Prior to this, he had been suffering from constipation. He was removed to a hospital where he improved, but one week later he suddenly had a "stroke" which affected his speech and the entire right side of the body. After this accident he remained at home for two years and then returned to school for a year. When at home he did out-door work or helped in a wholesale grocery. His general physical development was quite remarkable. Before the onset of his present illness he could lift sacks of sugar weighing 140 pounds without difficulty. Last spring the boy was advised to take up woodworking, and he became a carpenter's helper. However, instead of spending his time in the shop learning cabinet making as he desired, he was obliged to work outside, and his usual task was the digging of post holes. He suffered from generalized aching as a result of this exertion, but no dyspnea or symptoms of cardiac embarrassment. He thoroughly disliked the work, and his employer complained that he did not do enough. Before taking this job he had worked irregularly and was in the habit of sleeping very late each morning. During the latter part of April he was obliged to give up work because of weakness, generalized abdominal pain and fatigue. He was kept in bed for six weeks and given only a liquid diet. Three weeks before coming here he began to have frequent slight syncopal attacks. He had one severe attack when it was said that his face became black and he could not talk. When first seen here he complained that his "head got hot at times" and "things seemed to fuse together." Short spells of dizziness were frequent and also mild syncopal attacks in which "things seemed to float away." At no time while under observation did he faint or actually become unconscious.

Examination.—The boy's general appearance was normal and his muscular development was excellent. His usual weight was 140 pounds. There was still evidence of the former right hemiplegia. The right leg was dragged slightly when walking.

The right arm was held in an awkward position and movements were clumsy as though the arm were stiff, but there was no real spasticity. The reflexes on this side were increased, and there was a positive Babinski sign on the right foot. Strength was not impaired, and the right arm showed greater power than the left. The principal abnormal findings were in the heart. This was enlarged so that the left border was almost at the anterior axillary line. The total transverse diameter was 17.2 cm. There was a systolic murmur at the apex, and a short early diastolic murmur was heard in the fourth left interspace near the sternum. The first sound was of booming quality, and the pulmonic second sound was accentuated. There was no thrill. The fluoroscopic examination showed considerable enlargement of the left auricle in both the anterior and right oblique positions. The physical and roentgenographic examinations were indicative of advanced mitral stenosis, although the possibility of congenital heart disease must be considered. The blood pressure was usually low. The systolic varied from 90 to 128 mm. and the diastolic from 45 to 70 mm. The veins of the neck, head, and extremities were usually distended. Cyanosis was usually slight, appearing only in the finger nails. The lungs were normal and the vital capacity was 4150 c.c. At no time have signs of myocardial insufficiency been observed.

All of the many laboratory examinations made gave entirely normal findings. The blood calcium was 11.1 mg. per 100 c.c.

The mental status of this patient was decidedly abnormal, but difficult to classify. According to the Binet scale his mental age was fifteen years, a figure which seemed rather flattering. He was unstable, lacked power of concentration and was highly emotional. His lack of general knowledge could be accounted for in part by his limited schooling. A few examples of behavior will perhaps afford better insight into his character. When he first came to us, he exhibited a childlike interest in electric locomotives and made himself a nuisance to two corporations by his demands for photographs and drawings. Another interest was his trumpet, and almost daily he went to a near-by woods where he struggled with simple tunes. He again took up woodworking and spent hours in the carpenter shop gluing pieces of wood together. On his return home a shop was fitted for him, and this proved of definite therapeutic value, as he displayed some aptitude for woodworking on a small scale and has applied himself to it for months. These instances will suffice to indicate conduct that is certainly abnormal for a man of twenty-three years.

THE CARDIAC MECHANISM

The dominant cardiac rhythm was a pure nodal rhythm with a short R-P interval. Cases of permanent nodal rhythm are very rare and are of interest from the standpoint of that mechanism. Many examinations were made during the course of a year and a true nodal rhythm was the only one recorded. No explanation for a permanent nodal rhythm can be offered in this case, but it is reasonably certain that the vagus nerve was not responsible for it. When sitting quietly in the laboratory, the rate varied from 32 to 86 beats per minute. In a few records deflections were seen suggesting isolated auricular waves (Fig. 1, Lead III), but at no time was a ventricular response to an auricular impulse observed. The first electrocardiogram was taken on June 21. It showed a regular nodal rhythm, rate 69. To confirm the nodal rhythm, a record was taken the following day which is reproduced in Fig. 1. On June 29 many records were taken; periods of standstill varying from three to seven seconds occurred at frequent

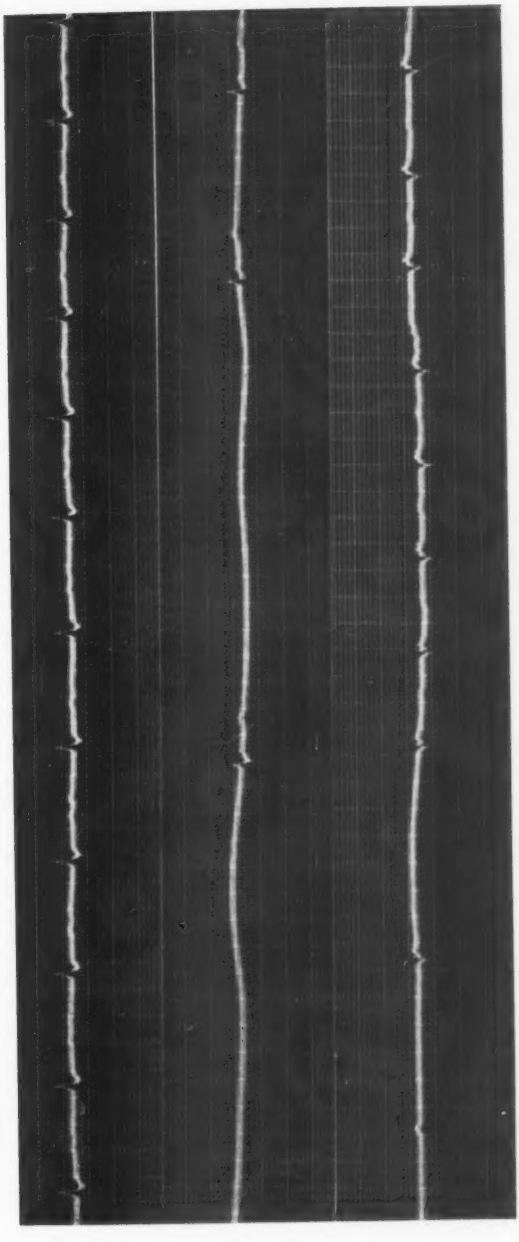

Fig. 1.—Electrocardiogram of June 22, 1928. Lead I, rate 74. Lead III, rate after pause, 83 per minute.

but irregular intervals. At several examinations made during July such pauses of the heart were always present. Then they disappeared, and the electrocardiograms made from July 18 to September 28 showed only nodal bradycardia with a rate varying from 32 to 54 beats per minute. During September the boy went home for one week. He said that after boarding the train the pauses in his pulse recurred and were frequent during his stay at home. After he returned to the clinic they disappeared promptly. On September 18 and on November 5, periods of standstill were again present. On the latter date their appearance followed an impulsive decision to return home immediately.

On days that these pauses were present the boy usually complained of slight dizziness and blurring of vision which occurred at irregular intervals. The only objective sign of the pauses was alternate paling and flushing of the skin, especially that of the face. Certainly one must conclude that cerebral anemia in this patient was very well tolerated. He was not always conscious of periods of standstill of the heart; on July 12, he said he felt very well and was not having pauses, but when electrocardiograms were taken, there were frequent periods of standstill of which he was not aware. Definite precipitating factors could be observed for some of these periods of standstill; at the first examinations they were apt to be preceded by a contortive bending backward of the trunk, and at the same time swallowing movements and deep irregular breathing were observed. On September 28, when electrocardiograms were being taken, if (from the galvanometer room) the boy were sharply commanded to sit still at a time when he was perfectly quiet and the heart was beating regularly, standstill of the heart invariably occurred. It had also been noticed that a scolding was apt to precipitate a series of pauses in the pulse. On those days when such pauses were present, they were by no means constant. They have been observed when the boy was applying to a nurse for some medicine for relief, and when he was seen a short time later on the street or in the carpenter shop, his pulse was regular, at a rate of 70 to 76 beats per minute. Even when standstill did not occur, on the taking of the pulse there was a marked fall of rate after the first ten seconds. On April 16, 1929, when the boy was becoming restless under the institutional regimen and was about to return home, the three variations of mechanism which he exhibited were recorded within less than ten minutes. It was as though constantly increasing vagal stimulation were being applied. The first record showed the usual nodal rhythm, rate 59 per minute; then periods of standstill were present for a few minutes, and these in turn were replaced by regular bradycardia, rate 36 per minute (Fig. 2).

The rates of beating at which standstill occurred varied from 63 to 86 per minute. In general the periods of standstill were longer with the slower rates of beating (58 to 70 per minute), indicating a rela-

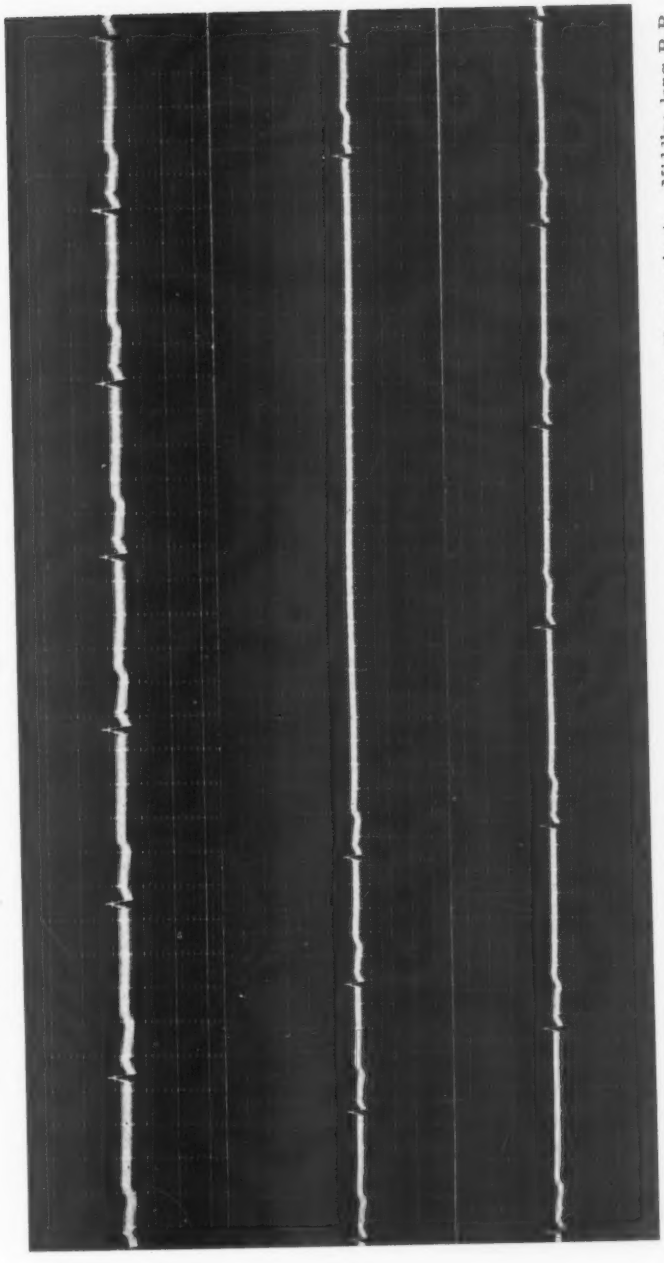

Fig. 2.—Records, (Lead II) of April 16, 1929, taken within ten minutes. Upper: rate 59 per minute. Middle: long R-R interval, 5.0 seconds. Lower: rate 36 per minute.

tively greater sustained increase in vagal tonus. They were never seen when the rate was under 45 beats per minute. Sometimes the period of standstill was preceded by slight slowing; more often it occurred abruptly. Likewise, the "pick-up" after the pause was prompt, and often the rate immediately following was slightly faster than that preceding the standstill. Occasionally after a pause of from three to four seconds a single beat was followed by a second pause, so that there was but one beat in a period of from seven to ten seconds. Only once in the many electrocardiograms taken was an altered ventricular complex seen which suggested ventricular escape.

Respiration.—On several occasions when periods of standstill were occurring, electrocardiograms and respiratory tracings were recorded simultaneously. No definite relation between respiratory movements and standstill could be ascertained. Standstill often occurred during quiet breathing, as well as after deep inspiration. At a time when periods of standstill occurred spontaneously they could be precipitated by having the patient hold his breath. But when there was present a regular bradycardia with a rate approximately 40 per minute, suspension of respiration did not cause either the appearance of periods of standstill or further slowing of the rate.

Exercise.—The response to mild exercise was always normal. Periods of standstill disappeared for a short time at least. The electrocardiograms taken on September 28 before and after exercise, which consisted of running up and down the corridor, are reproduced in Fig. 3. The rate before exercise was approximately 70 per minute with periods of standstill varying from five to six and five-tenths seconds. The rate of the first beats that could be recorded after exercise was 96 per minute; within ten seconds the rate of beating had fallen to 72 per minute. A few minutes later when the blood pressure was being taken, the pauses again appeared. On September 18, the rhythm was a nodal bradycardia, rate 41 per minute. After running down and up two flights of stairs the rate of the first recorded beats was 73 per minute; this declined rapidly to 60 per minute. The only change in the electric complexes was a decrease in the height of the R-waves at the rapid rate of beating.

Vagal Pressure.—Neither pressure in the neck over the carotid sheaths or pressure on the eyeballs produced any effect. The very attempt at such procedures resulted in a prompt fall in rate before actual pressure was applied.

Atropine.—On June 29, $\frac{1}{50}$ grain of atropine sulphate was given subcutaneously. The maximum rise in rate occurred after twenty minutes (Fig. 4). The periods of standstill disappeared ten minutes after the injection and did not reappear that afternoon. After the full atropine effect was obtained, neither deep breathing, holding a full inspiration nor any of the contortions which before always resulted in

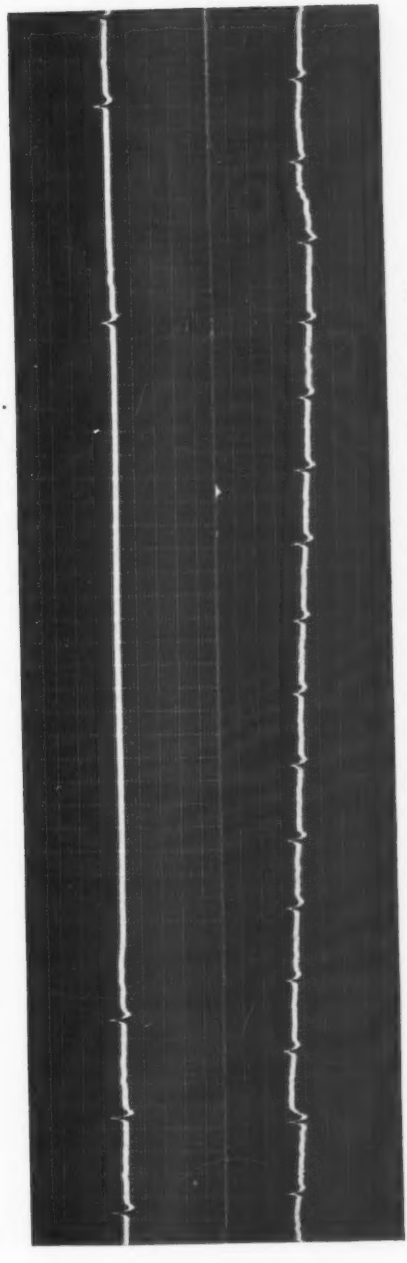

Fig. 3.—Records taken September 28, 1928, before and after exercise.

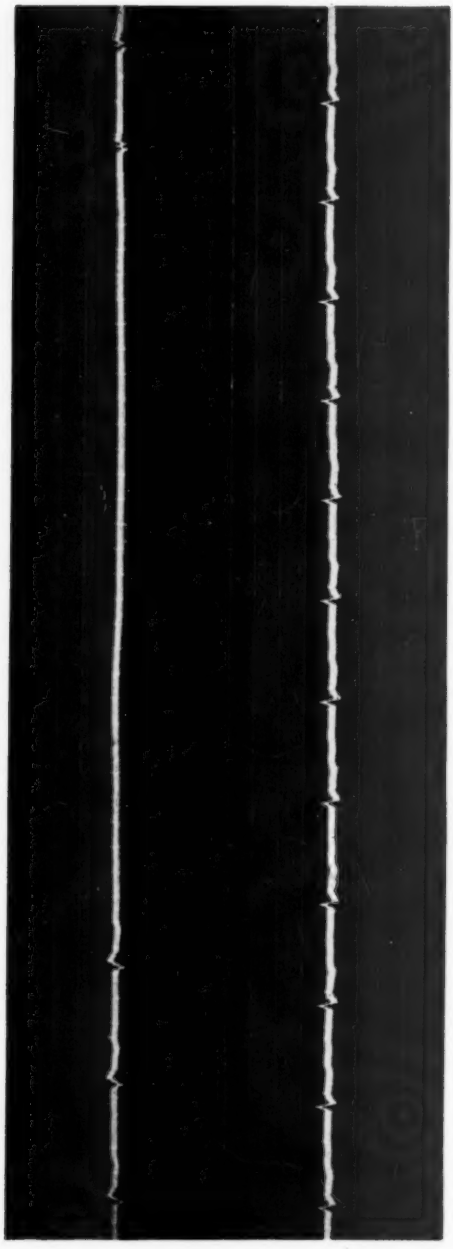

Fig. 4.—Records of June 29, 1928, before and after atropine. Long R-R interval, 6.6 seconds. Rate twenty minutes after 1/50 grain atropine sulphate, 83 per minute.

a period of standstill, caused a change in the mechanism. On August 4, $\frac{1}{50}$ grain of atropine sulphate dissolved under the tongue produced no effect whatsoever. The reaction to $\frac{1}{33}$ grain of atropine sulphate given on August 22 when nodal bradycardia was present is given in Table I. Of special interest is the definite rise in blood pressure.

TABLE I

REACTION TO ATROPINE

TIME	RADIAL RATE	BLOOD PRESSURE	E. K. G. RATE	REMARKS
2:15			39	Nodal rhythm. Slight irregularity.
2:20	42	100–48		Pulse irregular.
2:25			40	More regular.
2:30	40	95–48		
2:33	Atropine sulphate 0.03 grain (subcutaneous)			
2:48			85	No change in R-P interval.
2:53	86	120–70		
3:03			87	Face flushed.
3:08	84	128–80		
3:18			86	
3:20	82	116-76		
3:33			83	
3:37	80	110-75		Dryness of throat. Pupils widely dilated.

Epinephrin.—On August 10, nine minims of a 1-1000 epinephrin solution were given subcutaneously. This was without any definite effect; a rise in rate of six beats per minute occurred after one-half hour, but this may not have been due to the drug. On August 15, 1 c.c. of 1-1000 epinephrin solution was given, also subcutaneously. The initial rate of beating was 38 per minute. Eight minutes later the rate was 44 per minute and one extrasystole was recorded. Forty minutes after epinephrin the rate was 52 per minute; there was definite arrhythmia; the R-R intervals varied from 0.9 to 1.3 seconds; both P- and T-waves were larger. The blood pressure did not change during this observation. However, each time it was taken the boy leaned back and took a deep breath. It seemed that vagal tone was so great that it could readily offset any increase in sympathetic tone that might have been supplied by the epinephrin. Later, 1 c.c. of 1-100,000 solution was injected intravenously without any definite effect on either blood pressure or pulse rate.

COMMENT

The response of the cardiac mechanism to exercise and to atropine is conclusive evidence that both the high grade bradycardia and the standstill of the heart were of vagal origin. There remains to be considered only the question of the nature of the unusual inhibitory action. The boy had had a cerebral accident resulting in an hemiplegia. It seemed certain that this was due to a lesion in the internal

capsule and that there was no involvement of bulbar nuclei. That there could be any relation between this old injury and the present vagal disturbance seems very doubtful. There was no evidence of any lesion along the peripheral path of the vagus, as in one of Gerhardt's[1] cases, in which the left vagus nerve was imbedded in a tumor mass. Mackenzie[2] has reported standstill of the heart by vagal inhibition which resulted from digitalis medication. It is reasonably certain that drug was not a factor in the first periods of standstill that were observed. No digitalis was given during the following ten months, but periods of standstill were frequently recorded. In 1921, Wedd[3] reported a series of cases showing abnormal vagal tone which he thought had its origin in the diseased myocardium or aorta. Such a conjecture might be made in this case; organic disease was present, but in contrast to those earlier cases, the functional capacity of the heart was excellent at the time of the disturbance.

The question of an augmented vagal tone acting on a damaged conduction system may be considered. Structural changes or impaired nutrition in the A-V node or conducting system as a factor in the production of standstill of the heart seems, however, unlikely. The highest rates of beating, indicating increased rate of impulse formation in the A-V node, were seen after exercise, and at this time periods of standstill disappeared. If functional impairment in the structures concerned were a factor, some form of block should have appeared when the rate increased. The period of increased rate of beating which occasionally followed standstill was probably due solely to a decrease of vagal tone and not primarily to an improved nutritional state following the period of rest.

Perhaps the explanation of the disturbed mechanism is actually much simpler than has been implied in the foregoing paragraphs, and greater emphasis should be placed on the receptor than the stimulus. The fact that the dominant rhythm is nodal may be of prime importance. Lewis[4] states that "the influence of both vagi over rhythms emanating from the A-V node is powerful". But it can hardly be doubted that the patient had markedly enhanced vagal tone, and although considerable variation in the rate of impulse formation may occur, cessation of activity for periods of several seconds is not one of the attributes of nodal rhythm.

A search of literature has revealed very few case histories similar to the one reported here. Trocmé[5] has reported a patient with organic heart disease and periods of standstill of vagal origin, but no evidence was offered that the standstill was due to psychic factors. Laslett[6] described one instance without definite heart disease. As to the ultimate origin of the increased vagal tone he said one could express no decided opinion. Dejerine[7] states that emotions may produce syncopal crises. Gerhardt cited the case of a woman with a large heart and

disease of the conducting system in which he believed that syncopal attacks resulted from vagal stimulation and that psychic influence was the cause.

The case here reported was under almost continuous observation for ten months. Abnormal behavior of the cardiac mechanism has been so definitely related to emotional states that we feel that the only explanation for the disturbances, either the periods of standstill of the heart or the high grade bradycardia, that is consistent with all the known facts makes their origin a psychogenetic one. Because there was apparently a profound disturbance associated with organic disease, this explanation at first seems difficult to accept, but perhaps it will be less so if one bears in mind that it is not the character of the reaction but the degree that is unusual.

SUMMARY

A case is described which exhibited permanent nodal rhythm, with periods of standstill of the whole heart and of high grade bradycardia. The disappearance of these unusual disturbances of rhythm following exercise and atropine is proof of vagal origin. From a consideration of the mental and emotional make-up of the patient and of the circumstances associated with increased vagal tone it seems certain that the primary factor was a psychic one.

REFERENCES

1. Gerhardt, D.: Klinische und anatomische Beiträge über Adams-Stokes'che Krankheit und Vagusbradykardie, Deutsche Arch. Klin. Med. **106**: 462, 1912.
2. Mackenzie, Sir James: Diseases of the Heart, London, 1908, p. 345, Oxford University Press.
3. Wedd, A. M.: Neurogenic Irregularities of the Heart in Adults, Am. J. M. Sc. **172**: 49, 1921.
4. Lewis, Sir T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, p. 193, Shaw and Sons, Ltd.
5. Trocmé, P.: Étude des Accidents Syncopaux au cours des Arythmies, Paris, 1927, p. 65, Librairie le Françoise.
6. Laslett, E. E.: Syncopal Attacks, Associated With Prolonged Arrest of the Whole Heart, Quart. J. Med. **2**: 347, 1908-09.
7. Dejerine, J.: Sémiologie des affections du Système Nerveux, Paris, 1926, p. 1012, Masson et Cie.

ELECTROCARDIOGRAPHIC CHANGES IN QUIESCENT RHEUMATIC DISEASE IN CHILDREN AND YOUNG ADULTS*

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IN RECENT years there has been a lively interest in the electrocardiographic changes noted during acute rheumatic fever.[1-6] Several investigators have reported their work on this subject, and the conclusions drawn are quite similar. Pathologically, it is well known that in a number of instances the myocardium as well as the endocardium is involved in the acute process during rheumatic fever, but persistent evidence of these changes is often missing in post-mortem studies of chronic rheumatic heart disease. With the aid of the electrocardiogram, however, some evidence of change in the myocardium was found in almost every case of acute rheumatic fever during the acute stage. The electrocardiographic changes observed were of three main types:

1. Prolonged duration of the P-R interval, usually not to the degree of causing actual heart-block.

2. Alteration in the ventricular complex affecting either the QRS, the R-T, or S-T interval or the T-wave itself.

3. Numerous irregularities in cardiac rhythm.

Probably the most characteristic changes noted occurred in the R-T or S-T interval, these being of several different types. In some instances, the normal iso-electric period between the R-T or S-T wave was found shortened or entirely absent. Other tracings showed the R-T period coming off higher or lower than the base line. Occasional tracings showed what appeared to be an interruption of the R-wave so that the R-wave did not reach the base line but was apparently merged over with the T-wave, this change suggesting the wave described by Pardee[7] as a sign of blocking of the coronary artery. All these changes varied from time to time, and most of them disappeared, as the patients recovered from the acute stage of the disease. There was no correlation found between the electrocardiographic changes and the clinical findings. The average percentage of changes noted in the tracings by the several investigators was as follows:[5]

P-R in excess of 0.21 sec.	21.15 per cent
P-R in excess of 0.20 sec.	87.6 per cent
Changes in ventricular complex	63.5 per cent

*From the Lymanhurst School Heart Clinic, Department of Public Welfare, Minneapolis, Minn. Preparation of the illustrative material through the courtesy of the Department of Medicine, University of Minnesota.

Changes in S-T	Many to 42.4 per cent
Some change in the tracing	70.66 per cent
Extrasystoles	25.28 per cent
Dropped beats	7.7 per cent

The variations were found to be transient by most of the authors. Reid and Kenway found the changes transient in 15, or 57 per cent, of their cases. The conclusions drawn from these reports are that the changes found are characteristic of cardiac involvement but are not specific for rheumatic fever and that it will be necessary to study the cases over a longer period of time before these observations can be used clinically for diagnosis and prognosis.

Thus it seemed worth while to study the electrocardiographic changes during quiescent rheumatic disease in children and young adults who had apparently recovered from the acute rheumatic process. In following over a period of six years more than 300 children and young adults who gave a previous history of rheumatic fever or chorea or both, it was noted that the infectious process does not always cease when the patient is permitted out of bed but that definite signs of a low grade continuous infection are present. A large number of these children have almost a continuous rise of temperature to 100° F. or above; they have frequent attacks of "growing pains"; they have occasional attacks of a single swollen joint; leucocytosis of a low grade appears from time to time; the pulse is rapid at rest, and the children are often anemic. Electrocardiographic tracings were taken on 119 children who were attending the Lymanhurst School Heart Clinic. The tracings were repeated from time to time, but because of the character of the material it was not possible to obtain repeated tracings on all of the children. Twenty per cent of these children gave a history of rheumatic infection during the two previous years. Sixty-five per cent had their acute rheumatic disease within three years from the date of the first tracing. Eighty-seven, or 73 per cent, of these children had definite rheumatic heart disease, while thirty-two, or 27 per cent, showed no involvement of the heart as far as could be determined by clinical examination or x-ray. The majority had been confined to bed for varying periods of time, and in practically every case the diagnosis of rheumatic disease had been made by the attending physician. The tracings were all made at the Minneapolis General Hospital and for the most part were read by Dr. M. H. Nathanson of the staff of that hospital.

These tracings revealed the following findings:

1. *Changes in P-Wave.*—In five cases, or 4 per cent, a distinct notching in the P-wave was found in the first or second lead or both and also in five tracings, or 4 per cent, the P-wave was unusually high or peaked.

2. *Changes in P-R Interval.*—In ten patients, or 8 per cent, the P-R interval was prolonged to 0.2 sec. or more, but in no instance was this sufficient to produce an actual heart-block.

3. *Changes in QRS Complex.*—In four cases, or 3 per cent, the QRS period was notched at the peak in the first or second lead or both, and in four instances, or 3 per cent, the QRS was widened to 0.12 sec.

4. *Changes in R-T or S-T Interval.*—(Figs. 1 and 2.) In fifty-three cases, or 45.5 per cent, the isoelectric period was entirely absent, and the T-wave actually came off directly from the descending limb of the R-wave or the S-wave. In twenty-one, or 17.5 per cent, of the cases the R-T or S-T interval was definitely shortened; the rise was distinctly abrupt; there was practically no iso-electric period. The iso-electric period was either entirely absent or markedly changed from normal in

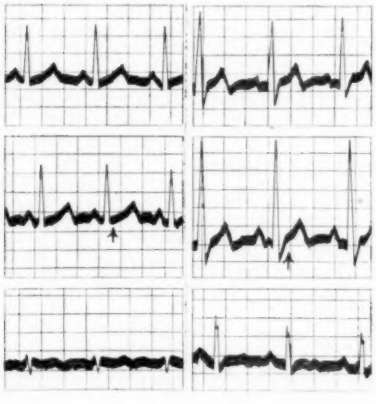

Fig. 1-*B*. Fig. 1-*A*.

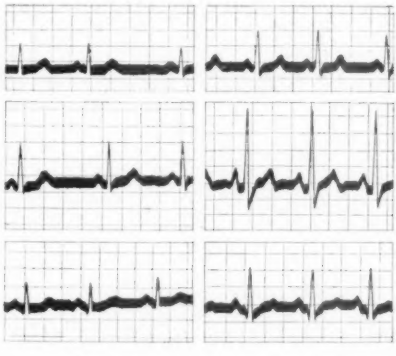

Fig. 2-*A*. Fig. 2-*B*.

Fig. 1.—Absence of normal isoelectric period between the R-T or S-T interval.
Fig. 2.—Tracings on one patient on different dates, showing variations in R-T or S-T interval.

63 per cent of the cases studied. In eighteen cases, or 15 per cent, the T-wave came off higher than the foot points of the R-wave, while in twenty-three, or 19 per cent, the T-wave had its inception lower than the base line. In ten tracings, or 8 per cent, the R-wave was interrupted in its progress toward the base line, the T-wave starting as a direct continuation of the interrupted R-wave, suggesting the change which frequently has been described as indicative of coronary occlusion (Fig. 3).

5. *Changes in the T-wave.*—In three instances the T-wave was negative in Leads I or II or both.

6. *Arrhythmia.*—Two instances of auricular extrasystoles and one of ventricular extrasystoles were noted as well as eight instances of sinus arrhythmia.

In order to determine whether or not these same changes might be present in tracings taken from children with normal hearts who gave no history of rheumatic infection a single tracing was taken on each of 50 children, who were examined in the Minneapolis Public Schools and found to have normal hearts and who gave no history of rheumatic disease. In none of the electrocardiographic tracings taken in this control group was the P-R interval prolonged to 0.2 sec., and there were no significant notchings or widening of the QRS complex.

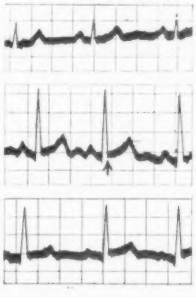

Fig. 3.—The descending limb of the R-wave does not reach the base line suggesting the change described as typical of coronary occlusion.

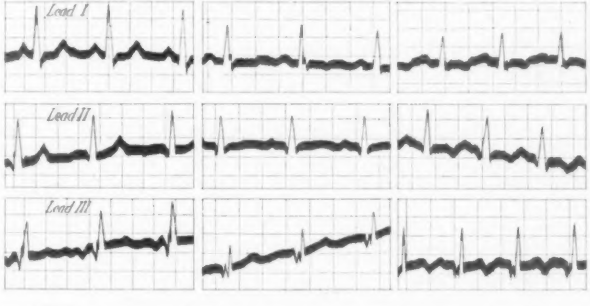

Fig. 4.—Tracings on one patient taken on different dates, showing changes in R-T or S-T interval as well as decided variations in the T-waves and some change in the QRS complexes.

In three instances the S-T interval was shortened more than is usually considered normal, but in none of this control group was there an entire absence of the iso-electric period between the R or S and the beginning of the T-wave. There were no inversions of the T-wave in Leads I or II, nor were there any irregularities in cardiac rhythm other than eight instances of sinus arrhythmia.

In order to determine whether or not the variations in the tracings found in acute rheumatic fever might also exist in tracings taken on children with quiescent rheumatic disease, twenty of these children, who gave a definite history of rheumatic infection, had repeated trac-

ings taken over a period of a year. A control group of ten of the normal children also had repeated tracings. This group is too small for statistical treatment; however, the differences between these two sets of tracings were striking. In the normal group the tracings remained practically unchanged, while those taken on the rheumatic group varied considerably from time to time. The P-wave became notched where before it was not notched; the S-wave became deeper in one or more leads; notching appeared in the QRS complex; the T-wave became diphasic, flattened or inverted where before it had been positive; the T-wave also in many instances came off higher or lower than previously, and there were also other minor variations in the S-T or R-T interval (Fig. 4).

It is, therefore, apparent that the variations in this quiescent rheumatic group are similar to the changes found by other investigators studying electrocardiographic changes during acute rheumatic fever.

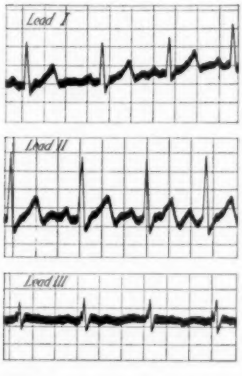

Fig. 5.—Tracing taken on March 12, 1928, when diagnosis was functional heart disease. This child subsequently developed a characteristic mitral stenosis. Shows absence of iso-electric interval between S- and T-waves especially well in Lead II.

DISCUSSION

The diagnosis of rheumatic carditis in the early stage is often solely dependent on the history of previous rheumatic infection, this being especially true when there is no cardiac enlargement. However, rheumatic disease is of such a variable nature that it is often difficult to evaluate symptoms presented as indicative of rheumatic disease. It is frequently difficult to decide whether or not a systolic murmur heard at the apex of a child's heart has any significance. The apical systolic murmur means more in a child than in an adult. It is not uncommon to follow children with such indefinite findings over a period of years and watch them develop into typical mitral stenosis with characteristic cardiac enlargement when in the beginning the murmur was considered as nonpathological and of no importance. As an example of such a case, the following might be cited:

A mother brought her child to the clinic, complaining that the child was not well, was pale, and had been sent home from school repeatedly because of fever, this rise of temperature having been more or less persistent over a period of weeks. Examination revealed a localized systolic murmur over the apex. The x-ray showed no enlargement of the heart, and we obtained no history of rheumatic disease nor even a history of "growing pains" or frequent tonsillitis. At that time we considered this case as functional heart disease and had the child examined carefully for a possible pyelocystitis. On re-examination a year and a half later we found a definite double mitral lesion with characteristic cardiac enlargement verified by x-ray. In this type of case the electrocardiogram would prove of more than theoretical value. In this particular instance, tracings taken when the child was first examined did show changes which were probably characteristic of rheumatic infection but were not recognized at that time (Fig. 5).

The study of tracings taken from children with quiescent rheumatic disease shows changes similar to those found during acute rheumatic fever, but the frequency of changes in the quiescent group was smaller. As in the active group, the changes varied from time to time. The most prevalent and most characteristic change noted was the absence of the isoelectric period between the S-T or R-T interval and the variability of this portion of the tracing. It is desirable to correlate the electrocardiographic changes with clinical evidence of continued rheumatic activity and to study these changes over a longer period of time.

SUMMARY

Electrocardiographic tracings were taken on 119 children giving a history of rheumatic disease who were able to attend school regularly; tracings were also taken on 50 normal children who were used as controls. Many of the tracings taken from the children in the so-called quiescent group showed changes similar to those found in acute rheumatic fever, but the changes were found less frequently. Repeated tracings taken from children in the quiescent group showed variations similar to those found in the acute group. In the control group the tracings did not vary. The most common and most persistent finding in this quiescent group was the lack of iso-electric period between the R- or S-wave and the T-wave and the marked variability of the R-T or S-T interval from time to time.

REFERENCES

1. Parkinson, J., Goose, A. H., and Gunson, E. B.: Heart and Its Rhythm in Acute Rheumatism, Quart. J. Med. **13**: 363, 1920.
2. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**: 1, 1924.
3. Swift, H. F.: Rheumatic Fever, Am. J. M. Sc. **170**: 631, 1925.

4. Rothschild, M. A., Sacks, B., and Libman, E.: Disturbances of Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, AM. HEART J. **2**: 356, 1927.
5. Reid, W. D., and Kenway, F. L.: Value of Electrocardiogram in Acute Rheumatic Fever, New England J. Med. **198**: 177, 1928.
6. McMillan, T. M., and Cook, A.: Electrocardiographic Changes Occurring During Rheumatic Fever, Atlantic M. J. **31**: 806, 1928.
7. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**: 244, 1920.

THE DENSITY OF THE SURFACE CAPILLARY BED OF THE FOREARM IN HEALTH, IN ARTERIAL HYPERTENSION, AND IN ARTERIOSCLEROSIS*

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THE permeability and extent of the capillary bed has a fundamental bearing on tissue nutrition. While the permeability of the capillaries has been studied extensively, little is known concerning the density of the capillary bed of different organs in normal persons, and practically no information is available on the possible variation in the number of capillaries in disease. Coincident with involutionary changes of the body, a reduction in the reserve functional capacity of all organs occurs. There is also shrinkage in the volume of the tissues. The following factors referable to the capillary system may be responsible for the involutionary changes in the body: *A*, insufficient blood supply to the normal capillary bed; *B*, progressive disappearance of the capillaries with the result that cell areas of increasing radius are supplied by a single capillary; *C*, a disturbance of normal tissue nutrition as a result of impaired capillary permeability rather than a decrease in the number of capillaries; *D*, inability of the nutritive substances to reach the cells in normal proportion as a result of increase in the intercellular (cement) substances between capillaries and specific tissue cells. It is possible that various combinations of the enumerated factors may be active.

The difficulty of estimating the density of the capillary bed of human post-mortem tissues is well recognized. This difficulty is considerable even in experimental animals in which the injection of dyes may be started during life.[1, 2] Quantitative studies on the capillary content of tissues at different ages and under various conditions have not been recorded.

PURPOSE AND PLAN OF INVESTIGATION

The aim of the study presented here was to compare the surface capillary bed of an arbitrarily chosen skin area of the body of subjects without vascular disease with that of a group of patients with arterial hypertension and a group of patients with advanced arteriosclerosis. Theoretically, progressive decrease in the number of capillaries may be responsible for elevation of blood pressure and for involutionary changes in the body. The skin was chosen for study because it shows

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involutionary changes with advancing age, as judged from the change in consistency and elasticity. Skin tissue also permits observations on its capillaries in man under natural conditions. Wetzel and Zotterman[3] counted the visualized skin capillaries of various skin areas of normal subjects.

All the individuals studied were fair-skinned. Three skin areas over the antecubital surface of the forearm were selected arbitrarily for observation. The forearm was chosen because it has a delicate skin area which is only slightly exposed to changes in temperature, light and trauma, and because it is possible to immobilize it in a position convenient for microscopic observations. The arm was prepared by washing with soap and water and applying microscope immersion oil to the area to be studied. With the patient in a horizontal position, the arm was extended between two sand bags and attached to the long supporting arm of a heavily built iron stand under a capillary microscope. In order to visualize all the capillaries, the skin was congested by applying above the elbow a maintained pressure of approximately 100 mm. of mercury, a pressure just above the patient's diastolic arterial pressure. The capillary counts were started when a red flush appeared on the arm, indicating that the minute vessels were dilated. Absence of flush indicated that the congestive pressure was above the level of the systolic pressure. Because the blood volume of the arm is above normal under this experimental condition, it may be assumed that all the surface capillaries became filled with blood. This arrangement permits comparison of the capillary content of corresponding skin areas of different individuals under identical experimental conditions.

The first area (Skin Area A) observed was located 7 cm. below the epicondylar line over the lower angle of the antecubital space. The second area (Skin Area B) was 12 cm. below the epicondylar line, or approximately midway between the elbow and wrist joint. The third area (Skin Area C) was 3 cm. proximal to the lower border of the radius.

The capillaries were counted through a ruled disc inserted over the lens of the ocular of the microscope. A calibration indicated that 1 sq. mm. of the disc corresponded to 2.3 sq. mm. of skin area. After a little experience, only occasional difficulty was encountered in distinguishing the superficial capillaries from the subcapillary venous plexuses. Obviously, the microscope and forearm had to be in fixed position. Repeated counts over the same area showed a variation of less than 10 per cent as a rule. At least 5 counts were made over an area of 2.3 sq. mm. on each of the three skin areas. In addition to the capillary count, the capillaries of the nail bed were examined for their shape and for the nature of the blood flow.

To prove whether or not the presence of epidermis interferes with the visualization of the capillaries, small blisters were raised with cantharidin plasters over the upper portion of the forearm in five patients and the count over the blistered area was compared with that of the immediately adjacent area.

OBSERVATIONS

Table I indicates that the epidermis does not interfere with the counting of the capillaries.

TABLE I

COMPARATIVE COUNTS OF THE CAPILLARIES OF THE SKIN WITH AND WITHOUT THE PRESENCE OF THE EPIDERMIS

PATIENT NO.	AGE	DIAGNOSIS	NORMAL SKIN AREA CAP. PER SQ. MM.	BLISTERED SKIN AREA CAP. PER SQ. MM.
1	14	Post-rheumatic fever	30	33
2	51	Duodenal ulcer	25	27
3	59	Arteriosclerosis	25	26
4	60	Arteriosclerosis	35	33
5	60	Hypertension, arteriosclerosis	30	27
6	75	Hypertension, arteriosclerosis	28	28

Table II presents the capillary count over the three areas of the forearm of 20 control subjects with a normal cardiovascular system. Table III presents the counts of 20 patients with elevated arterial blood pressure: six of the patients suffered from essential hypertension without evidence of arteriosclerosis; the other 14 patients showed varying degrees of soft sclerosis of the peripheral arteries which probably resulted from a persistent high blood pressure. All the patients of this group had enlarged hearts. Table IV includes the capillary counts of 20 patients with senile arteriosclerosis but without hypertension or cardiac enlargement.

The capillary distribution in the patients with arteriosclerosis showed a rather marked irregularity and "moth eaten" appearance. The capillary loops of the nail bed showed irregularities, and the arterial portion of the loop was often narrow and hairlike in the patients with elevated blood pressure.

DISCUSSION

The results of these observations indicate that the capillary count was distinctly higher in the distal portion of the skin areas in both the control subjects and in the patients. The average capillary count varied between 25 and 58 per sq. mm. with an average of 35 in the normal subjects; between 22 and 49 per sq. mm. with an average of 35 in the group of patients with elevated blood pressure; and between 17 and 39 per sq. mm. with an average of 30 in the senile arteriosclerotic group.

TABLE II

THE EXTENT OF THE SURFACE CAPILLARIES OF THE SKIN IN 20 CONTROL SUBJECTS WITHOUT HYPERTENSION OR ARTERIOSCLEROSIS

SUBJECT NO.	AGE, YEARS	CONDITION	ART. BL. PR. SYST. MM. HG.	ART. BL. PR. DIAST. MM. HG.	AREA A CAP. PER SQ. MM.	AREA B CAP. PER SQ. MM.	AREA C CAP. PER SQ. MM.	AVERAGE COUNT CAP. PER SQ. MM.	VELOCITY OF CAP. BLOOD FLOW	TORTUOSITY OF CAP.
1	12	Post-rheumatic Fever	108	86	22	23	31	25		
2	14	Post-rheumatic Fever	118	84	25	30	38	31	Normal	Normal
3	15	Normal	108	70	29	31	38	33	Normal	Normal
4	16	Diabetes	116	74	27	31	32	29	Normal	Normal
5	16	Normal	112	66	31	38	43	37	Normal	Normal
6	23	Post-rheumatic Fever	136	109	23	32	45	31	Normal	Normal
7	23	G. C. Urethritis	142	88	31	33	40	35	Normal	
8	24	Post-rheumatic Fever	116	72	24	30	39	31	Normal	Normal
9	28	Post-rheumatic Fever	110	45	30	28	30	29		Normal
10	32	Aortitis	106	78	34	43	57	45		
11	35	Duodenal Ulcer	114	84	23	25	41	30	Slow	Normal
12	42	Toxic Hepatitis	120	76	28	33	46	36	Slow	Normal
13	44	Gastric Ulcer	112	78	19	33	50	34		
14	45	Psychoneurosis	116	19	25	33	41	33	Slow	Normal
15	45	Psychoneurosis	122	82	29	35	49	38	Normal	Normal
16	47	Dengue Fever (?)	92	64	31	37	55	41	Normal	Normal
17	47	Normal	114	40	34	35	50	40	Slow	Normal
18	50	Sinusitis	108	80	28	37	47	37	Normal	Normal
19	50	Pellagra	116	80	50	52	72	58		Normal
20	51	Duodenal Ulcer	98	66	20	28	32	27	Normal	Normal
Average	32.9		114.2	73.0	28.2	33.4	43.8	34.6		

TABLE III

THE EXTENT OF THE SURFACE CAPILLARIES OF THE SKIN IN 20 PATIENTS WITH ARTERIAL HYPERTENSION

PATIENT NO.	AGE, YEARS	SECONDARY DIAGNOSIS	ART. BL. PR. SYST. MM. HG.	ART. BL. PR. DIAST. MM. HG.	AREA A CAP. PER SQ. MM.	AREA B CAP. PER SQ. MM.	AREA C CAP. PER SQ. MM.	AVERAGE COUNT CAP. PER SQ. MM.	VELOCITY OF CAP. BLOOD FLOW	TORTUOSITY OF CAP.
1	18	Rheumatic Heart Disease	170	100	29	32	40	34	Rapid	Normal
2	38	None	202	110	34	39	45	39	Normal	Normal
3	40	None	210	100	30	36	38	35	Rapid	Slight
4	41	Nephrosclerosis	156	108	23	33	46	34	Rapid	Marked
5	42	None	220	120	33	38	50	40	Normal	Slight
6	42	None	204	112	27	32	41	35	Rapid	Normal
7	43	Arthritis	158	110	23	27	36	29	Rapid	Marked
8	48	None	228	105	30	36	39	35	Rapid	Slight
9	52	Nephrosclerosis	196	115	29	28		28	Rapid	Normal
10	59	Cirrhosis of Liver	182	114	27	35	54	39	Rapid	Normal
11	60	Arteriosclerosis	210	110	30	36	43	36	Slow	Normal
12	62	Obesity	152	88	36	43	55	45	Rapid	Normal
13	62	Emphysema	208	100	28	28	47	34	Rapid	Normal
14	62	Cardiac Asthma	174	104	30	33	50	37	Rapid	Marked
15	64	Obesity	160	84	26	27	44	34	Rapid	Marked
16	68	Myocardial Degeneration	162	74	35	37	75	49	Slow	Normal
17	75	Arteriosclerosis	162	100	26	39	42	36	Normal	Normal
18	76	Arteriosclerosis	170	100	22	21	23	22	Normal	Normal
19	84	Arteriosclerosis	170	100	20	38	50	36	Normal	Normal
20	84	Arteriosclerosis	162	94	18	18	44	27	Rapid	Normal
Average	56		182.8	102.4	27.8	32.8	45.4	35.2		

TABLE IV

THE EXTENT OF THE SURFACE CAPILLARIES OF THE SKIN IN 20 PATIENTS WITH ARTERIOSCLEROSIS AND NORMAL BLOOD PRESSURE

PATIENT NO.	AGE, YEARS	SECONDARY DIAGNOSIS	ART. BL. PR. SYST. MM. HG.	ART. BL. PR. DIAST. MM. HG.	AREA A CAP. PER SQ. MM.	AREA B CAP. PER SQ. MM.	AREA C CAP. PER SQ. MM.	AVERAGE COUNT CAP. PER SQ. MM.	VELOCITY OF CAP. BLOOD FLOW	TORTUOSITY OF CAP.
1	50	Tabes Dorsalis	104	70	29	25	28	27		Normal
2	50	Sinusitis	124	74	26	30	39	32	Normal	Normal
3	51	Auricular Fibrillation	138	84	28	33	52	38	Slow	Normal
4	52	Alcoholic Neuritis	130	80	29	35	38	34		
5	52	Cerebral Thrombosis	114	80	35	34	42	37	Normal	Normal
6	54	Obesity	110	80	27	35	48	37	Normal	Marked
7	59	Post Pneumonia	128	75	22	25	42	29		
8	60		137	77	17	17	18	17	Slow	Normal
9	60	Scurvy	146	68	21	24	38	28	Rapid	Normal
10	61	Pernicious Anemia	114	68	31	35	50	39	Normal	Normal
11	62	Cerebral Hemorrhage	112	80	24	32	49	35	Slow	Marked
12	62	Fibroid Tuberculosis	94	68	25	25	40	30	Normal	Normal
13	65	Auricular Fibrillation	120	76	26	28	37	30	Rapid	Normal
14	68		130	84	25	29	33	29	Normal	Normal
15	70	Diabetes	144	68	23	27	39	29	Normal	Marked
16	70	Alcohol Addiction	134	80	27	26	31	28	Normal	Marked
17	71		136	84	20	24	32	25	Slow	Marked
18	73		124	70	30	35	37	34	Slow	Normal
19	72		134	80	24	24	30	26	Normal	Normal
20	74	Post Pneumonia	104	74	23	27	29	26	Rapid	Normal
Average	61.8		123.8	76.0	25.6	28.5	37.6	30.5		

The variations in the counts within the groups were considerable, but no more than in certain circulatory functions. These variations are the more natural since the count of the surface capillaries is not necessarily an index of the number of capillaries per c.mm. of skin. The graphic representation of the distribution of the counts (Fig. 1) exhibits no definite difference between the three groups of individuals. The average count of the arteriosclerotic group is slightly lower than that of the control or hypertensive group. The distribution curve of the capillary contents of the arteriosclerotic group is shifted slightly to the left as shown in Fig. 1. No relationship existed, nevertheless, between the capillary counts and the clinical evidence of arteriosclerosis. Similarly, no relationship existed between the counts and the age of the patients. The average capillary count for subjects between ten and twenty-nine years of age (shown in Tables II, III, and IV) was 33 per sq. mm.; for subjects between thirty and forty-nine years

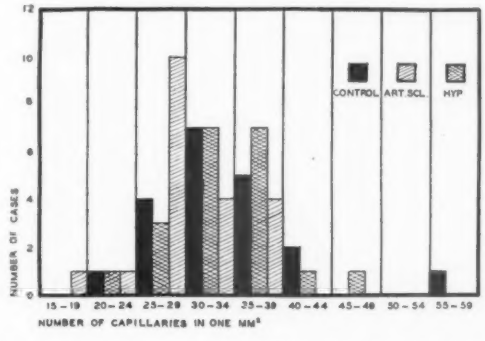

Fig. 1.—Graphic representation of the distribution of the extent of the surface capillary bed of the forearm in control subjects with a normal vascular system and in patients with arterial hypertension or with arteriosclerosis.

of age, 36 per sq. mm.; and for subjects between fifty and eighty-two years of age, 33 per sq. mm. The average count found in normal subjects was 33. The value found by Wetzel and Zotterman for the forearm was 43 per sq. mm. Their counts apparently were performed over the lower portion of the forearm.

The results of the study presented here indicate that reduction in the number of visible surface capillaries per square unit cannot be held responsible for the changes observed in the skin with advancing age and in arteriosclerosis. The radius of the cell area supplied by a single surface capillary may be the same in an aged individual with sclerosed larger vessels and inelastic, shrunken, thin skin as that in a young adult with elastic, smooth, normal skin. Since change in the number of capillaries per sq. mm. must be eliminated as a factor responsible for the involution of the skin, the responsible causes are probably among the other possibilities described above. The observation that the number of capillaries per sq. mm. is essentially the same

in patients with severe arteriosclerosis as in healthy young subjects, does not rule out definitely the possibility that a progressive decrease in the capillaries occurs with advancing age or with arteriosclerosis. If such a state of affairs exists, however, it must follow, in view of our findings, that with the loss of function of the capillaries the cells supplied by these capillaries disintegrate, and hence shrinkage of tissue follows. Thus the number of capillaries per sq. mm. remains essentially unaltered. Whether a reduction of the capilary bed and an increase of tissue radius supplied by a single capillary is not occasionally responsible for morbid changes in tissues cannot be stated from the observations presented.

CONCLUSIONS

1. The extent of the surface capillary bed of the skin of the forearm was essentially the same in a group of control subjects without vascular disease and in patients with arterial hypertension or arteriosclerosis.

2. Progressive involutionary changes of the skin cannot be explained on the basis of an increase in the radius of cell areas supplied by the surface capillaries.

REFERENCES

1. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, 1922, Yale University Press.
2. Wearn, J. T.: The Extent of the Capillary Bed of the Heart, J. Exper. Med. **47**: 273, 1928.
3. Wetzel, N. C., and Zotterman, Y.: On Differences in the Vascular Coloration of Various Regions of the Normal Human Skin, Heart **13**: 358, 1926.

Department of Clinical Reports

LOCALIZED SWEATING, A SYMPATHETIC REFLEX PHENOMENON IN ANGINA PECTORIS

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AMONG the less usual and more interesting manifestations of angina pectoris are those symptoms the underlying mechanism of which appears to be a sympathetic reflex are connecting the heart and aorta with visceral organs or glandular tissue. The following is the report of such a case.

CASE REPORT

A robust, somewhat florid physician of sixty-one years was seen ten days after having been awakened at 3 A.M. by severe precordial pain radiating into the left arm, lasting one hour, requiring morphine for relief. The patient had suffered two similar attacks six and two years previously. After the first attack the patient remained in bed three days and returned to his practice after five days, though he experienced precordial pain or substernal gripping on hurrying, usually relieved by rest. This passed away after four months and he tolerated strenuous exercise, even playing tennis without discomfort. After the second attack two years before, the patient led a somewhat less strenuous life though continuing in active practice. With all three attacks he noted light-colored stools and uneasiness in the right upper quadrant.

Both parents of the patient were long lived, dying at seventy-nine and eighty-eight years respectively. One brother died of heart disease at sixty-two. One sister now has hypertension. The patient had rheumatic fever lasting one week at thirty years of age. He had influenza with pneumonia in 1918. Answers to routine questions as to previous symptoms were negative except for some indigestion, consisting chiefly of gas after meals. There was no history of frank gall bladder attacks, jaundice, or constipation.

The physical examination was negative aside from a few râles at the bases. The examination of the heart was as follows: Cardiac dullness to percussion in the fifth space was 11 cm. to the left, 2.5 cm. beyond the midclavicular line. The left border of the heart was 7 cm. to the left in the third space. The transverse supracardiac dullness was 6.5 cm. There was a moderate to loud systolic murmur heard over the precordium, best heard at the apex. The rate was 90 and a well-marked gallop rhythm was noted. The blood pressure was 145 mm. mercury systolic and 110 diastolic. Alternation of the pulse was observed.

During absolute rest in bed the patient suffered some precordial distress and some indigestion with gas. On one occasion he had pain and tenderness in the right upper quadrant and gaseous eructations during the night. This recurred the next morning after taking a cup of coffee and was accompanied by pain in the left upper chest radiating into the arm.

The most interesting symptom of which this patient complained occurred two weeks after the onset of the third attack. He awoke to find the precordium, left

shoulder and left arm to the elbow drenched with sweat. The body was of normal moisture elsewhere. There was no pain, pressure or heaviness. He noticed that his pulse rate was somewhat accelerated.

Mackenzie[1, 2] noted flushing or sweating of forehead or body with attacks of angina. Vomiting, salivation, gaseous eructations and increased flow of urine were also observed by him. Vaquez[3] mentions fleeting vasomotor phenomena in angina pectoris, such as diffuse redness of hands and forearms accompanying or preceding the attack, and refers to observations by others of this flushing extending to face and chest.

Misch and Lechner[4] have recently reported two cases showing a sympathetic reflex similar to that reported in the present case except that the area of hyperhidrosis was the left side of the face supplied by the upper two branches of the trigeminal nerve. One of these patients had luetic heart disease, aortitis, aortic regurgitation and angina pectoris. The second patient was diagnosed as coronary sclerosis and angina pectoris. Both patients showed dilatation of the left pupil.

These same authors refer to two other cases. One of these, similar to the subject of the present report, was described separately by Conzen[5] and Bittorf.[6] A woman forty-six years of age had attacks of angina pectoris and occasionally with these attacks flushing and sweating of the left side of the face. The left pupil was twice as large as the right and was known to have been so for ten years. Gibson's[7] patient was a man forty-five years old who complained of constant pain in the left upper back and chest and in the arm with exacerbations of greater severity, relieved by amyl nitrite. This patient showed prominence of the left eye and dilatation of the left pupil, changes of which were more marked during attacks of pain. There was no sweating or skin changes except some pallor during an attack. The patient's symptoms improved under potassium iodide. X-ray examination of heart and great vessels was negative.

These cases clearly represent a reflex from the heart or aorta to the sweat glands, or ciliary muscle in those showing dilatation of the left pupil, conveyed by the sympathetic system and passing from the cord in the lower cervical and upper dorsal region,[8] which experimental and clinical research has shown is the pathway in typical anginal pain of the usual distribution. Head[9] produced a unilateral reflex hyperhidrosis in certain cases of gross cord injury, the stimulus being somatic, such as scratching or pinching the skin. The reflex in the above cases is evidently initiated by a visceral stimulus, namely anemia of the myocardium or a stimulus arising from aortic disease.

Recently the gastric and abdominal manifestations of angina pectoris and the differential diagnosis between cardiac and abdominal disease have claimed the attention of clinicians.[10, 11, 12, 13, 14] It is certainly very likely that a similar sympathetic reflex, the end organ

being in the abdominal viscera, is responsible for the disordered function giving rise to the symptoms. A very common and familiar manifestation is the indigestion characterized by gas, sour eructations and heartburn which so often accompanies attacks of angina pectoris or occurs with fatigue or slight overexertion in patients subject to anginal attacks. The mechanism is probably a sympathetic reflex from heart or aorta causing pylorospasm.

SUMMARY

One case is reported and three cases are quoted from the literature representing an unusual sympathetic reflex phenomenon in angina pectoris, which consists of localized sweating.

REFERENCES

1. Mackenzie, Sir James: Angina Pectoris, London, 1923, p. 84, Henry Froude.
2. Mackenzie, Sir James: Diseases of the Heart, London, 1925, ed. 4, p. 337, Oxford University Press.
3. Vaquez, H.: Diseases of the Heart. Translated by Laidlaw, G. F., Philadelphia, 1924, p. 410, W. B. Saunders Co.
4. Misch, W., and Lechner, A.: Ueber ein kardio-sympathisches Reflexphänomen, Klin. Wchnschr. **8**: 500, 1929.
5. Conzen, F. A. H.: Ueber die periphere Sympathicusaffektion insbesondere ihre Aetiologie und Symptomatologie, Leipzig, 1904, B. Georgi.
6. Bittorf, A.: Zur Symptomatologie der Aortensklerose, Deutsche Arch. f. klin. Med. **81**: 65, 1904.
7. Gibson, G. A.: Some Hitherto Undescribed Symptoms in Angina Pectoris, Brain **28**: 52, 1905.
8. Swetlow, G. I.: A Clinico-Pathological Study of the Pathway of Pain Impulses in Cardiac Disease, Am. J. M. Sc. **178**: 345, 1929.
9. Head, M.: Studies in Neurology, London, vol. 2, p. 491, 1920, Oxford University Press.
10. Faulkner, J. M., Marble, H. C., and White, P. D.: Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, J. A. M. A. **83**: 2080, 1924.
11. Foster, N. B.: Clinical Pictures of Cholecystitis Induced by Bacterial Endocarditis, M. Clinics N. America **9**: 325, 1925.
12. Riesman, D.: Myocardial Disease and Its Gastric Masquerades, J. A. M. A. **91**: 1521, 1928.
13. Friedenwald, J., and Morrison, T. H.: Clinical Observations on Relation of Gastric and Cardiac Affections, Southern M. J. **21**: 453, 1928.
14. Palmer, R. S.: Case Records of the Massachusetts General Hospital, New Eng. J. Med. **200**: 145, 1929.

LOCALIZED SWEATING REPLACING CARDIAC PAIN*

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THE following case is reported because it illustrates the occurrence of sympathetic reflex sweating in a patient with anginal pain. It is interesting to note that the sweating was strictly limited to the region where the patient had felt pain on effort for twenty-five years, but that the sweating occurred while the patient was at rest and not with the pain.

CASE REPORT

A.J.N., a retired clerk, aged 75 years, was admitted to the New York Hospital (service of Dr. L. A. Conner) on November 20 and died on December 21, 1926. He had rheumatic fever at 25 and at 27 years, being sick for six or eight weeks with each attack, and later had two milder rheumatic attacks. He never had syphilis, but had gonorrhea twice as a young man. At the age of 30 he was told that his heart was affected, but he had no symptoms and considered himself in excellent health until the age of 50. From then until the time of his death he suffered from dyspnea and anginal pain on exertion, and because of these symptoms he entered the New York Hospital eleven times, attended the out-patient department regularly, and on two occasions was admitted to Roosevelt Hospital.

His first admission to the hospital was in November 1908, when he complained of precordial pain and tenderness brought on by exertion. At this time he had a transient auricular fibrillation and fairly well marked sclerosis of his peripheral arteries. The heart was somewhat enlarged and there were systolic murmurs at the apex and aortic area, and at times a diastolic murmur heard to the left of the sternum. He remained in the hospital for six weeks. His next admission was in December 1914, when he complained of severe precordial pain brought on by exertion and radiating down the left arm. Blood pressure was not elevated, arteriosclerosis was marked, and the auricular fibrillation had become permanent. He was readmitted in 1916, 1917, 1918, 1919, 1920, 1921, 1924, and in March and November 1926, each time with the same complaints. On one admission he had a pulmonary embolus and on another an attack of jaundice. In November 1920 he was in the Neurological Institute because of a cerebral accident resulting in right hemiplegia, from which he made an almost complete recovery. In December 1926, while in the hospital, the patient had a sharp chill followed by fever and associated with transient hematuria. Chills and fever recurred daily; no local evidence of infection could be found, but a staphylococcus aureus was recovered from the blood stream; the patient grew progressively worse and died after two weeks. Permission for autopsy was not obtained.

The physical signs changed little in the last twelve years of the patient's life. The blood pressure was never elevated; the heart was somewhat enlarged, with the apex in the 5th space 10.5 cm. to the left of the midline. The rhythm was totally irregular. Systolic murmurs were present at the apex and the aortic area, and at times a soft diastolic murmur was heard to the left of the sternum in the 2nd, 3rd

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or 4th space. Retinal and peripheral arteries showed evidence of sclerosis. The Wassermann reaction was negative on repeated examinations. The electrocardiogram showed auricular fibrillation with left axis deviation and no abnormality of the ventricular waves. The records were practically identical over a period of ten years, a finding which was considered unlikely in the presence of any progressive disease of the coronary arteries.

On each admission to the hospital, and indeed on each visit to the clinic, the patient's complaint was the same. On exertion he became short of breath and had severe pain and pressure under the sternum, in the left side of the chest, radiating down the left arm and up into the left side of the neck. In 1914 the pain radiated to the jaw and left side of the face over the eye and was accompanied by a sense of pulsation in the left temporal region. Generalized sweating accompanied the more severe attacks of pain. In 1918 pain in the throat and hoarseness were noted with the pain. In 1921 the attacks were more frequent and were often followed by pain behind the left ear. Until 1926 the pain was always brought on by effort and relieved by rest; it started under the sternum, spread over the left side of the chest, radiated to the left arm and left side of the neck, and was commonly associated with hyperaesthesia of the skin. In March 1926 the patient stated that he had had several attacks of pain at night, and on admission to the hospital the whole precordial area was sensitive to light touch. On March 29 the following note was made: "Last night patient had a very profuse localized sweat limited to the area where anginal pain occurs,—i.e. precordium, left shoulder and left arm. He has had similar experience two or three times before coming to hospital. Sweat occurs at night and is not accompanied by pain." At this time the pupils were equal and there was no flushing or other vasomotor disturbance. After six weeks of rest the patient went home and was fairly comfortable for six months, but in November he re-entered the hospital for the last time. On December 2 the following note was made: "About once in 24 hours, while sleeping and usually at night, patient complains of profuse sweating of the left side of chest, left arm and left side of neck. It corresponds to the same area where he has previously complained of anginal pain. He rarely has pain with the sweating." There was no change in the signs at this time, but a few days later the patient developed the acute infection from which he died.

COMMENT

A case is reported in which localized sweating occurred, apparently as a substitute for anginal pain. The sweating was limited to the region where the pain had previously been felt and was observed repeatedly in the last year of the patient's life. It was not accompanied by exophthalmos, dilatation of the pupil or other evidence of sympathetic involvement. Cardiac pain was present for the last twenty-five years of the patient's life and was believed to be related to an old rheumatic valvular disease. The patient had generalized arteriosclerosis but no evidence of progressive coronary disease.

PERMANENT BRADYCARDIA FOLLOWING DIPHTHERIA, CASE REPORT*

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BOSTON, MASS.

THE occurrence of heart-block is well known in severe cases of diphtheria. The development of this arrhythmia is of serious import and often is followed by the death of the patient. In the experience of an authority[1] on diphtheria, the patients who survive the onset of heart-block for a week have a good chance to recover, and in this type of case deaths never occur after two weeks. In the majority of cases, if the patient survive the acute attack, the heart after a few months is perfectly normal even to electrocardiographic examination.

There are but few reports in the literature of the occurrence of a permanent arrhythmia resulting from diphtheria. There is one report of permanent auricular fibrillation,[2] following heart-block; and two of complete heart-block which remained permanent in spite of the recovery of the patient from the diphtheria. The first[3] was a woman of twenty-three years in whom the diphtheria occurred nineteen years previously; the second,[4] also a woman, aged forty-eight, had survived the diphtheria forty-two years. To these I wish to add the report of a case of permanent bradycardia.

CASE REPORT

An American schoolgirl, aged ten years.

Past History.—Had measles, whooping cough and German measles. At the age of 4 years while living in Japan she suffered an attack of "Japanese jaundice." Nausea was the chief symptom, and she was able to eat little for one week. The jaundice persisted from two to three weeks; recovery was apparently complete.

At the age of five years, and after her return to the United States, she contracted a severe attack of diphtheria, which confined her to bed for two and one-half months. Sixty thousand units of antitoxin were administered, the first dose being given on the second day of the illness. There were many complications. Her parents stated definitely that the rate of their daughter's heartbeat suddenly dropped on the seventh day of the diphtheria and the rate has remained slow ever since. There was a "dragging of the legs" following the diphtheria and this rapidly disappeared during the first six weeks of her convalescence, about four months after the onset of the diphtheria. One year later a pediatrician in Chicago noted a slow heart rate, which he believed would gradually disappear, and no other abnormalities.

She never had any form of rheumatism, or chorea, or tonsillitis save at the time of the diphtheria.

Present Illness.—She appeared well and strong subsequent to recovery from the diphtheria. One week ago, however, after running about a half mile she collapsed

*From the Evans Memorial Hospital for Medical Research and Boston University, School of Medicine.

and appeared to be unconscious for a period of about three minutes, and then rapidly recovered. She slept for the next hour. There were no other attacks. She was a very active child and played normally with other children. She was examined by Dr. H. C. Petterson, who noted the bradycardia and referred her for study.

Physical Examination.—A well-developed girl. The heart appeared normal in size. There was a soft systolic murmur with the first sound over the midprecordia.

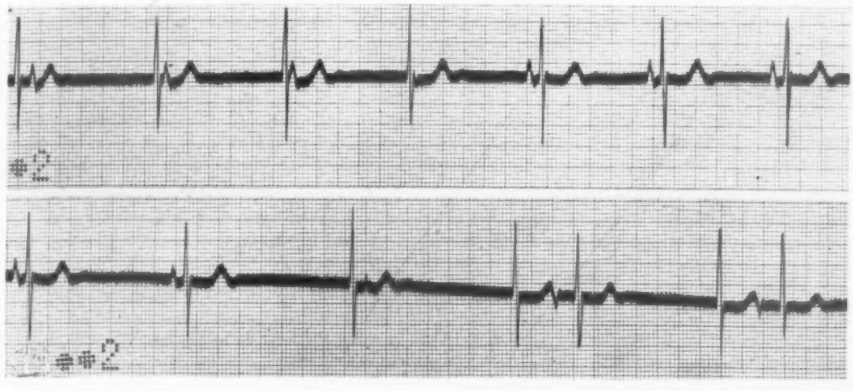

Fig. 1.—Sections of Lead II taken March 9, 1929. Above: ventricular rate 48; definite P-waves are present and show a progression from a position following to one preceding the QRS complex. Below: ventricular rate 46-50; the P-waves are less constant in form; they are absent after the initial three ventricular complexes; toward the end of this strip coupling occurs; the premature beats are preceded by inverted P-waves.

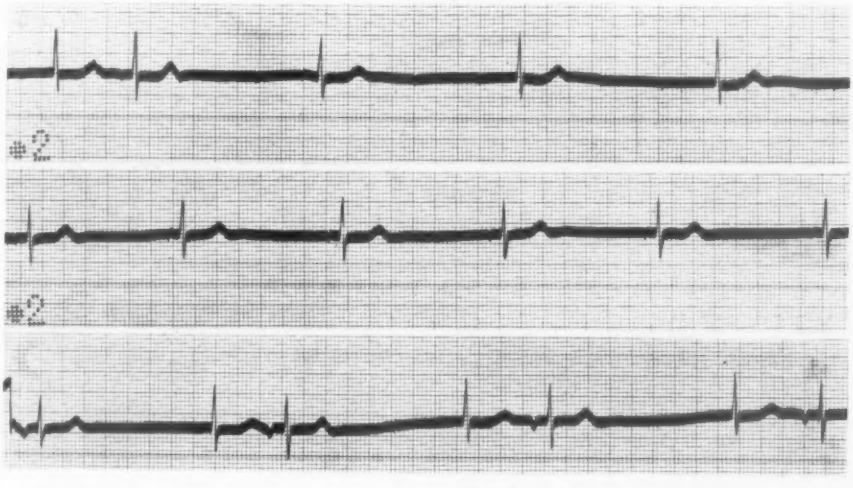

Fig. 2.—Sections of Lead II taken July 9, 1929. Top: ventricular rate 32; there are traces of what may be a P-wave at a rate of about 110. Middle: after exercise; ventricular rate 39; a trace of a P-wave occurs 0.12 second before each QRS complex. Bottom: after exercise; ventricular rate 52; coupled rhythm is present; the second beat of each pair is preceded by an inverted P-wave.

The heart rate was 48, and after rising from the horizontal to the sitting position six times the rate was 42 per minute. There were periods when the beats occurred in pairs, as in coupled rhythm, and occasionally there appeared to be a single extrasystole. The remainder of the cardiac and general physical examination was normal.

Subsequent History.—There have been no further attacks of syncope. She leads a normal life, but has been advised to avoid strenuous exertion such as the long run.

Electrocardiograms.—Electrocardiograms were obtained at the time of first examination on March 9, 1929, and on July 9, 1929. At the latter date records were obtained at rest and after exercise, such as sitting up and lying down and hopping on one foot.

Selections from the electrocardiograms are given in the accompanying illustrations. The interpretation of these electrocardiograms is not obvious. The tracing obtained on March 9 contains a definite P-wave which might be thought to indicate an impulse from the sino-auricular node, but its evident time relationship to the ventricular complex at such a slow rate and its position sometimes subsequent to the QRS make it more likely that the impulses start from the A-V node. The top strip of Fig. 2 depicts a rate of but 32 which is consistent with idioventricular rhythm; the rate is somewhat higher in the other two and it is probable that the impulses are initiated at a higher level, as in the A-V node. The sole strip which suggests complete dissociation, in case the minute waves are considered to be P-waves, is the top record of Fig. 2. The almost complete disappearance of the P-waves in the electrocardiogram of July 9 is noteworthy.

Study of the entire electrocardiograms obtained on these two occasions warrants the conclusion that there is little if any activity of the sinus node. Exercise in the laboratory failed to accelerate the ventricular rate above about 50 per minute; this result agrees with the clinical observations of the effect of exercise, of both Dr. Petterson and myself.

DISCUSSION

I have both examined and taken an electrocardiogram of the patient reported by Drs. White and Jones and at the time was inclined to doubt the explanation of the complete heart-block as due to diphtheria. It is well known that heart-block may be congenital or acquired and of unknown etiology.[5] However, knowledge of the additional case reported by Read[4] and observation of the case described herein makes me ready to accept all three as due to diphtheria. The history in this last patient is convincingly definite.

The case now reported differs from the others in that there is little evidence of activity of the sinus node; the electrocardiograms of the two adult patients show typical examples of complete heart-block with the auricles beating at a higher rate than that of the ventricles. In my patient the impulses appear to emanate from varying levels of the A-V tissues.

It is also noteworthy that the exercise tolerance was essentially normal in all three patients. The attack of syncope occurring in the little girl after running the half mile may have been due to the Adams-Stokes syndrome. Such explanation appears the more probable from the electrocardiographic evidence of the shifting of the impulse center up and down the junctional tissues, which may be inferred to be damaged by the attack of diphtheria.

It has already been stated that if the patient survives the acute attack of diphtheria, the heart eventually becomes normal both to clinical and electrocardiographic examination. That there are occasional

exceptions to this is suggested by the case now reported and the few cited from the literature. A quotation from one of the most exhaustive studies of the pathology of diphtheria offers support to this opinion. Referring to the heart, Councilman[6] *et al.* state: "Acute interstitial lesions of two sorts are found. In one there are focal collections of plasma and lymphoid cells in the tissue, which may be accompanied by degeneration of the myocardium, but are not dependent upon it. This condition is analogous to acute interstitial nephritis. In the other condition, the interstitial lesion consists of a proliferation of the cells of the tissue and is secondary to the degeneration of the muscle. It is probable that this may lead to extensive formation of connective tissue and some of the cases of fibrous myocarditis may be due to this."

SUMMARY

The occurrence of permanent arrhythmias of the heart is rare after recovery from diphtheria. A case is reported of permanent bradycardia appearing during the course of a severe attack of diphtheria. Electrocardiograms disclosed the impulse center to be the A-V node and junctional tissues, with a shifting of the pacemaker between these locations. As far as I am aware, there are reports of but two other cases similar to the one herein reported, and the latter stands alone in certain respects.

REFERENCES

1. Place, E. H.: J. A. M. A. **77**: 771, 1921.
2. Parkinson, J.: Auricular Fibrillation Following Complete Heart-Block in Diphtheria, Heart **6**: 13, 1915.
3. White, P. D., and Jones, T. D.: The Heart After Severe Diphtheria, AM. HEART J. **3**: 190, 1927.
4. Read, J. M.: Heart-Block—Complete, Compensated, Calif. and West. Med. **31**: 1, 1929; and J. A. M. A. **93**: 1125, 1929.
5. Reid, W. D.: Intermittent Partial Heart-Block. Report of a Case, J. Lab. & Clin. Med. **13**: 734, 1928.
6. Councilman, W. T., Mallory, F. B., and Pearce, R. M.: A Study of the Bacteriology and Pathology of Two Hundred and Twenty Fatal Cases of Diphtheria, J. Boston Soc. M. Sc. **5**: 139, 1900.

Department of Reviews and Abstracts

Selected Abstracts

Schwartz, Sidney P., and Schwedel, John B.: Digitalis Studies on Children with Heart Disease. II. The Effects of Digitalis on the Sinus Rate of Children with Rheumatic Fever and Chronic Valvular Heart Disease. Am. J. Dis. Child. **39:** 298, 1930.

The purpose of this study was to determine the effects of digitalis on the sinus rate of children with rheumatic heart disease and signs of heart failure and to point out the relationship between the slowing of the sinus rate when present and the relief from symptoms.

Tincture of digitalis was administered in daily doses of 3 c.c. to 12 such children until the appearance of nausea and vomiting. A progressive slowing of the sinus rate was noted in all 7 children who were kept in bed after they had received from 3 to 9 c.c. of the drug during the inactive phase of the disease.

Nausea and vomiting developed in all children as a very late manifestation of digitalis action, after the use of from 24 to 50 c.c. of the drug; whereas slowing of the sinus rate was a very early effect which appeared progressively from the first day. Furthermore sinus bradycardia the only type of slowing of the heart rate which could be considered of therapeutic value was a transitory phenomenon in all children never lasting more than four to seven days at the most. A further reduction in the heart rate was due to heart block.

The authors believe that since there is no quantitative relationship between sinus bradycardia and the appearance of nausea and vomiting the latter cannot be used as a criterion in estimating the optimal therapeutic dose of digitalis for children with chronic rheumatic valvular heart disease.

Schwartz, Sidney P.: Digitalis Studies on Children with Heart Disease. III. Auricular Fibrillation in Children with an Early Toxic Digitalis Manifestation. Am. J. Dis. Child. **39:** 549, 1930.

Two children are reported to whom digitalis was administered during an active bout of rheumatic fever because of several signs of heart failure, such as enlargement of the liver and swelling of the face with ascites.

In one child, aged six and one-half years, the daily administration of 3 c.c. of the tincture of digitalis resulted in a progressive increase of the P-R interval with dropped beats and the development of auricular fibrillation after a total of 24 c.c. of the drug had been given within eight days. Nausea and vomiting did not appear until the development of the fibrillation. Death resulted seven hours after the establishment of the arrhythmia. In another child, aged eight and one-half years, auricular fibrillation, with a slow ventricular rate and alternate premature beats of the ventricles, developed after 32 c.c. of the tincture had been administered within nine days. The fibrillation appeared before the premature ventricular beats and disappeared within six days.

In both instances, the development of the fibrillation was considered the result of vagal stimulation by the drug during a period of active carditis.

Because of the dangers involved in the administration of digitalis during active carditis, it is concluded that digitalis is contraindicated in such children with rheumatic fever and signs of cardiac insufficiency.

Whitten, Merritt B.: A Comparison of the Blood Supply of the Right and Left Ventricles in Childhood. Arch. Int. Med. **45**: 46, 1930.

By means of celluloid injection and corrosion specimens of the heart, the author has studied the distribution of the blood vessels to the ventricles of the heart in a series of specimens from children.

It was found that at birth and during the latter part of fetal life the right and left ventricles are about equal in vascularity. By the end of the second year the left ventricle has become definitely more vascular than the right. This preponderance increases until about the tenth year of life, after which no increase in the vascular preponderance of the left ventricle could be demonstrated. There is definite preponderance of the venous circulation in the left ventricle as compared with that of the right.

Whitten, Merritt B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction. Arch. Int. Med. **45**: 383, 1930.

By means of injection and corrosion specimens of the heart, the author has studied the relation of the coronary vessels in thrombosis and myocardial infarction. Approximately 40 hearts have been injected and studied. The deep branches of the arteries of the left ventricle leave at right angles and pass directly through the myocardium. The branches of the arteries of the right ventricle spread out in practically the same plane as the larger artery from which they arise. The fact that the injury in infarction is almost always to the left ventricle, whereas the right ventricle rarely is involved seems to depend on the differences in the anatomic structure of the arteries of the two ventricles.

The author believes that the branches that leave the surface vessels at right angles to penetrate the myocardium appear to immobilize the main arteries. This immobilization or anchoring of the main vessels appears to augment its tortuosities possibly leading to kinking or constriction with consequent diminution of its lumen at the point of narrowing.

The author has found that besides the relative absence of anchoring by deep branches the right coronary artery as it swings around the right side of the heart, describes an almost complete semicircle. He believes that this is a protection to this part of the right coronary artery.

Infarction in the posterior surfaces of the left ventricle is much more common than has been heretofore recognized. Infarction at the apex may be due occasionally to occlusion of the right coronary artery.

Infarction in the right ventricle was found only in connection with massive infarction and usually was minimal in amount. The right ventricle although it appears to be less vascular than the left it is not believed to be especially predisposed to failure with age. In fact, the left ventricle is found to be the one to fail most frequently from arterial insufficiency.

Conner, Lewis A.: The Psychic Factor in Cardiac Disorders. J. A. M. A. **94**: 447, 1930.

In approaching the subject of the psychic factor in cardiac disorders the author considers this factor first in relation to cardiac neuroses and later in connection with organic disease of the heart. He believes that the psychogenic stimulus arises either from an unfortunate statement of some physician or life insurance examiner; from the occurrence of some dramatic case of heart disease perhaps with sudden death, among the relatives or friends of the patient; from the appearance of some symptom which calls the attention of the patient to his heart and leads to a doubt as to its integrity; or from some profound and pro-

tracted emotional disturbance such as deep grief or prolonged anxiety in which, however, there is at first no element of doubt concerning the state of the heart. He believes that this group of patients represents a most important type of individual requiring special care and handling. Such management of these patients with cardiac neuroses belongs essentially to the realm of psychotherapy. The details of such treatment will, of course, vary with the character of the individual patient and with the predilections of the physician.

The second group is of patients in whom the psychic factor originates in those with organic heart disease. The physician is called on to exercise great discrimination and judgment in differentiating between the symptoms which are the legitimate result of the existing organic disease and those which are merely the expression of the associated psychic upheavals. The physician must know from experience just what is to be expected in the way of symptoms from the type and grade of the organic lesions present.

In discussing the treatment of these patients, the author believes that prophylaxis is of very great importance. Exercise, the occasional use of drugs, the advisability of rest in bed, baths and massage are all discussed.

Wenckebach, K. F.: The Use of Foxglove at the Bedside. Brit. M. J. No. 1, 181, 1930.

In this address the author discusses the use of digitalis at the bedside without instrumental observation. Briefly he states that digitalis is indicated in all cases of heart failure, that is, where insufficient functioning of the heart is the cause of the pathological condition. This holds good irrespective of the cause of the heart failure itself. He follows the old custom of using large, medium and small doses, a distinction which needs no special explanation and is easily followed at the bedside. The only requirement is to adopt a certain unit of activity which may be the basis of this dosage. The author is strongly in favor of the use of dried leaves of digitalis by mouth.

As adjuvants in digitalis treatment the author discusses the use of caffeine and caffeine diuretics. He also believes that the new mercury preparations novasurol and salyrgan at the right moment and in the proper dosage constitutes perhaps the greatest recent progress in the treatment of heart patients. The resulting depletion of the body relieves the overfilled circulation, lessens the circulatory resistance and frees the heart and kidneys from a great part of their task so that it smooths the way for better action by the foxglove.

Diet and venesection are mentioned.

As adjuvants in regulating the heart rhythm the author discusses both strychnine and quinine. He believes that a combination of strychnine and quinine is followed by immediate and lasting success in cases of extrasystolic irregularities without marked heart failure. He cites the instance of a friend with aortic incompetence extremely miserable during the periods of extrasystolic beats who was relieved by strychnine and quinine.

In discussing prolonged digitalis administration he discusses the use of very small doses and larger doses.

Josef, V. Boros: Changes in the Electrocardiogram Following Transient Changes in Conduction. Wien. Arch. f. innere med. **19:** 339, 1929.

This article is a report of two cases showing transient changes in the electrocardiogram. The first case is a fifteen-year-old school boy who in the course of an acute infection showed partial heart block and Wenckebach's periods. The ventricular complexes resembled those usually seen in right axis deviation; that is, low S waves in Lead I, and inverted T-waves in Leads II and III. The fol-

lowing day he had completely recovered. The A-V conduction time was now normal and the ventricular complexes now had diphasic T waves in Lead II, and positive T-waves in Lead III. Later still the ventricular complexes became completely normal. The author interpreted these changes as being transient disturbances of intra-ventricular conduction.

The second case was a sixty-two-year-old man with degenerative heart disease and congestive heart failure. He showed two to one heart block with an auricular rate of 160 and a typical P-wave. As he recovered, his auricular rate slowed down and his heart block disappeared. He now showed normal upright P-waves with increased conduction time (0.30 seconds). The author interprets this return to normal as a result of improved conduction through the auricles, while the auricular rate was slowed.

Fahr, Th.: Contribution to the Question of Rheumatic Granulomatosis. Klin. Wchnschr. **8**: 1995, 1929.

This is a discussion based on a case description and refers to the fact that rheumatic nodules may be found both in the pericardium and in the tonsils, and in the tissues surrounding the joints.

The author is of the opinion that these lesions are as specific as those of tuberculosis or Hodgkin's disease and therefore suggests the name Rheumatic Granulomatosis for the disease which we have hitherto known as rheumatic fever. He discusses the pathogenesis of the disorder and believes that the streptococcal element of both rheumatic fever and of scarlet fever is superimposed upon the original condition, the nature of which is ill understood, but which probably is allergic in origin. He emphasizes that rheumatic fever may be found without Streptococcus viridans and that the organism may be found in persons who have no other evidence of rheumatic infection.

Ionescu, Von Prof., and Raileanu, C.: Experimental Investigations on the State of the Cardiac Muscle after Extirpation of the Stellate Ganglion. Wien. Arch. f. inn. med. **19**: 199, 1929.

The author removed the stellate ganglion on one or both sides of the neck of rabbits and dogs. The animals recovered completely from the operation and in their behavior showed no difference from healthy animals with whom they were running about. The operation produced no change in the microscopical section of the heart muscle.

Thirty to 380 days after the operation, the sections showed no histological changes neither of inflammatory nor of degenerative nature. Nor were any histological changes observed in the periaortic or pericardiac ganglia.

Palmer, Robert Sterling: The Significance of Essential Hypertension in Young Male Adults. J. A. M. A. **94**: 694, 1930.

The author reports that in 3598 records of physical examinations done from the department of hygiene of Harvard University it was found that slightly more than 10 per cent of those examined showed systolic blood pressure about 140 mm. of mercury and 2.25 per cent of the whole group showed systolic pressures of 150 or more without other abnormalities. The urine examination in all instances was negative. The systolic pressures were all more than 10 per cent above the level expected when height, weight and age were taken into consideration. Approximately half of these individuals showed diastolic pressures more than 10 per cent above the calculated normal while only one-fourth of a normal control group showed an elevation in the diastolic pressure. A large proportion of nervous and neurotic types was found among those showing systolic pressures

above 140 and among those showing pressures between this level. There was no correlation between the infectious diseases or constipation and hypertension in this series as compared with a normal series of equal size.

One hundred and fifteen persons, 66 from the normal control series and 49 from those showing hypertension were followed over an interval of ten years. Of the 66 normal individuals, 3 or 4.54 per cent had systolic pressures over 140 and one had a systolic pressure of 150. Of 49 subjects who showed pressures over 140 at the first examination, 12.2 per cent showed systolic pressures between 140 and 150 after ten years and 10.2 per cent showed systolic pressures of 150 or over, the highest being 180. Thus if hypertension is found at twenty years of age it is somewhat more likely to be found persistent after ten years than it is to develop during this interval.

Those showing hypertension at the original examination ten years or more earlier when followed give a history of vasomotor symptoms in one-fourth of the cases as compared with such a history in one-seventh followed from the normal group.

The incidence of cardiovascular disease in the family histories of a normal control and the hypertensive groups was approximately the same.

White, Paul D., and Churchill, Edward D.: The Relief of Obstruction to the Circulation in a Case of Chronic Constrictive Pericarditis. New Eng. J. Med. **202:** 165, 1930.

A review of the condition of the heart and pericardial sac in chronic adhesive pericarditis together with the progress of the patient leading up to the signs and symptoms of cardiac embarrassment is presented and discussed. Various types of operations that have been devised for the relief of this cardiac embarrassment are briefly described.

A case herein reported is of particular interest because of the striking benefit that resulted during the year following the operation of pericardial decortication. The operation performed was as follows: five costal cartilages from the third to the seventh inclusive were resected with short portions of the fourth and fifth ribs. Through this approach with the left pleura retracted laterally, the pericardium was exposed. It was found to be much thickened and scarred and it firmly enclosed the heart which was obviously unable to pulsate freely in its grip. A sheet of pericardium about the size of the palm of the hand was resected from the anterior aspect of the heart. At once the heart expanded through this gap in the rigid pericardial membrane and its pulsations obviously increased in extent and freedom. The left side of the sternum was cut away with rongeurs and the dissection of the pericardium was continued a short distance further as far as the right auricle. Finally a constricting band with calcareous nodules kinking the inferior vena cava just above the diaphragm was discovered and resected allowing the great vein to resume its normal calibre. At the end of the operation the muscle and skin flaps were brought back into position over the exposed heart.

During the past year since the operation, the patient has continued her steady improvement so that now she lives a perfectly normal life for a girl of her age, nineteen years. She has been able to walk several miles a day, to dance, and even to run for trains without undue shortness of breath. The etiology of the pericarditis in this case is unknown.

Tallerman, Kenneth H., and Jupe, Montague H.: Displacement of the Heart in Pneumonia in Childhood. Arch. Dis. Child. **4:** 230, 1929.

Five cases are described in which during an attack of pneumonia the heart deviated toward the side of the lesion subsequently returning slowly to a normal

position as recovery occurred. A consideration of these cases and of other similar cases reported in the literature points to the fact that this phenomenon is not infrequent in childhood and would in all probability be more often noted if specially looked for by physical examination and if radiograms of the chest were taken early. Displacement of the heart appears to be brought about by the traction exercised by shrinkage due to partial collapse of the affected lung, aided by the push of the sound lung which is frequently distended by compensatory emphysema.

This cardiac displacement is not caused by a pulling over due to fibrosis, since it occurs in the acute stage of the disease and the heart subsequently returns to its normal position. Moreover, neither by physical nor by radiological examination can evidence of fibrosis be noted.

McLean, C. C.: Early Rheumatic Infections of Childhood. Arch. Ped. 46: 657, 1929.

The author reports 118 cases of early rheumatic infection seen in private practice in Birmingham, Alabama, during the past eight years. There were 51 boys and 67 girls included in the study. The age of greatest frequency was from five to eight years. The most common symptoms presented by the patients when first seen were poor appetite, failure to gain weight, nervousness, fatigue, repeated attacks of tonsillitis and nasopharyngeal infection, and pain in the legs, joints or stiffness of limbs. Forty-four children had tonsils and adenoids removed when the diagnosis of rheumatic infection was made but most of these cases gave a history of repeated attacks of tonsillitis and suggestive symptoms of a rheumatic infection before the operation. There were signs and symptoms of mild chorea in 42 of the children. Of the 118 cases 84, or 71 per cent, had soft blowing systolic murmurs. These murmurs were heard in 52.3 per cent of the chorea patients and in 81.5 per cent of the 76 who had no signs of chorea. Apparently there was little or no hypertrophy of the heart.

Of the 118 children there were 103 underweight for their height. There were 35 of the 118 cases who developed symptoms and physical signs of rheumatic infection while under observation. Many of these children were original feeding cases who had been under care throughout their lives. There were 92 cases in which the foci of infection was thought to have been located in tonsils, teeth, sinuses, ears, or nasopharyngeal tissue.

The author describes in brief the management instituted in the care of each of these children. He stresses rest in bed and removal of foci of infection. Several case reports are included.

In conclusion, he believes that every child with manifestations of an early rheumatic infection is a potential cardiac patient and should be managed accordingly.

Coates, Vincent: The Relation of Orthodox Rheumatic Infection to Multiple Infective Arthritis. Brit. M. J. 1: 67, 1930.

By orthodox rheumatic infection the author means frank rheumatic fever and by multiple infective arthritis he means that type of subacute or chronic arthritis which is nonsuppurative and is due to an infection of a nonspecific character.

He has studied the possible relationship between these two conditions by the following methods:

1. The evidence afforded by the family history of fifty consecutive cases of multiple infective arthritis in regard to orthodox rheumatic infection. In 16 instances rheumatic fever was known to have occurred in a parent, brother or

sister. He believes that this incidence of 32 per cent accords with the popular conception that "rheumatism" has a familial or hereditary basis.

2. The incidence of a clear history of orthodox rheumatic infection in 300 consecutive cases of multiple infective arthritis. Rheumatic fever is believed to have occurred in 14 instances.

3. The occurrence in the aforesaid 300 cases of cardinal signs of orthodox rheumatic infection, namely, cardiac lesions and subcutaneous nodules. In the 300 cases 4 per cent showed cardiac lesions and 6 per cent subcutaneous nodules.

Rothman, Phillip E.: Digitalis Therapy. Its Use in Children. California & West. Med. **30:** 150, 1929.

The author discusses briefly and completely the indications, methods of administration, and signs of digitalization in children. He believes that children apparently fall into the category of individuals whose vagus centers are more easily stimulated than usual or whose hearts are unusually susceptible to the slowing action of the vagus. He believes that there is a tremendous individual variation in the tolerance of children that makes a detailed examination of the patient an absolute necessity before the administration of the next dose.

Herrick, James B.: Atypical Features of Acute Coronary Occlusion. Ann. Int. Med. **3:** 105, 1929.

The picture of acute coronary occlusion must not be drawn with too fixed lines. Allowance must be made for many variations from the ordinary type, for mild and subacute cases, for cases without pain, for instances of extreme variation in blood pressure, degree of dyspnea, temperature, pulse rate and rhythm. One must see as well cases with early or late embolic accidents, for recurrence due to proximal increase in the thrombus or to involvement of new vessels. If all this is done, the condition will be recognized more frequently even than now and probably a larger percentage of deaths from angina pectoris will be shown to be due to this accident in the coronary artery.

Coombs, Carey F.: The Diagnosis and Treatment of Rheumatic Heart Disease in Its Early Stages. Brit. M. J. **1:** 227, 1930.

In this British Medical Association Lecture, the author discusses many of the features of rheumatic heart disease in children particularly in a group of 653 children with rheumatic heart disease seen in a cardiac clinic. He believes that progress in the treatment of these children depends on the same principles as those involved in the fight against all infections, *early* diagnosis and *persevering* treatment. If rheumatic injury to the heart is to be recognized in an early stage, it can only be done by remembering that symptoms of cardiac insufficiency do not appear till the lesions are already established and severe.

He believes there are four different approaches to a diagnosis of cardiac rheumatism in its early stages.

1. The easiest of these is that in which the rheumatic infection declares its presence within the body by provoking either arthritic pains or chorea. He believes that pain persisting more than a day or pain which makes the child lame ought to be noticed, also that if the child looks ill or has a rise of temperature, however small, with pain a physician should be seen. He believes that every child who has rheumatic polyarthritis that can be recognized as such may be assumed to have an infected heart also even if there are neither symptoms nor signs of this.

2. Rheumatic carditis is so often preceded by an attack of tonsillitis that one ought to consider repeated examination of the heart an essential part of the care of any child with inflamed tonsils. He believes that children convalescent from tonsillitis ought to be seen a few days after every obvious symptom has cleared up.

3. The most important of all these methods of securing an early diagnosis of cardiac rheumatism is that which it is hardest to practice and easiest to forget; the fact that the heart may become definitely and permanently damaged by rheumatic infection without any other perceptible manifestation of the infection. Of 1100 children referred to the cardiac clinic by the School Medical Service for an opinion on the state of the heart, 653 have been judged to be suffering from rheumatic heart disease. During the same period in the same city, 238 cases of heart disease have been reported from private practice of medical men. It seems, therefore, as if for every case of rheumatic carditis that makes itself known to a medical man at the time when it is established, there are two that are not found until the child is examined as a part of the school routine. In order to recognize such cases early, the author believes that early symptoms of heart disease are not cardiac but constitutional; loss of appetite, vague "seediness," increased pallor and above all loss of weight.

4. Finally there are a few children in whom the first symptoms point to heart disease. These children fall into two groups. First, those who are taken with an acute febrile illness with chest symptoms. Second, another group who are brought in because of breathlessness. This is a very small group, because it takes a severe degree of cardiac disease to make a child visibly breathless. Whether the carditis is acute or chronic, it must be severe if it is to produce symptoms of cardiac insufficiency.

The author devotes considerable time to a discussion of cardiac arrhythmias and murmurs made out in these children. He discusses the mistakes that may be made in paying too much attention to these signs alone.

Finally, he discusses the treatment of these children. This may be summed up chiefly in providing complete rest in bed at home or in convalescent institutions. He discusses briefly the use of salicylates.

Miller, Reginald: The Diagnosis of Early Juvenile Rheumatism. Brit. M. J. 1: 230, 1930.

The author discusses the symptoms and signs of early juvenile rheumatism under four main headings. He doubts the existence of a rheumatic diathesis and believes that rheumatism in these children is an environmental disease. He also has no liking for the term "prerheumatic child." He believes that a prerheumatic child is the ordinary rheumatic child who has not yet suffered a knock-out attack of the infection.

The first group of symptoms discussed are those of a constitutional nature. He believes that rheumatism is the result of a generalized systemic infection and that the child is inclined to show a general ill health. Such a child is pale, sallow, unhealthy in appearance, poor appetite, irritable nerves, poor sleep, occasional cough and shortness of breath. The child's most important symptom usually is fatigue. He discusses the similarity of these symptoms to a tuberculous infection.

The second group is the most easily recognizable group of children with sore throats and pain in the joints. He discusses the relationship of infected tonsils to these children, particularly the advisability of tonsillectomy.

The third group shows symptoms referable to nervous instability and actual chorea. He is inclined to believe that a rheumatic child becomes nervous even though actual chorea is not present.

The fourth group is made up of children who show signs in the heart indicating rheumatic infection. The signs most suspicious of rheumatic heart disease are as follows: (a) increased pulse rate, (b) dilatation of the left ventricle, (c) the presence of an apical systolic murmur with enlargement of the left ventricle, (d) presence of a reduplicated apical second sound or of a mid-diastolic apical murmur.

Wedd, A. M. and Hubbard, R. S.: Notes on Dosage and Excretion of Quinidine Sulphate. Clifton Med. Bull. **15**: 69, 1929.

The authors have made qualitative tests of the excretion of alkaloid in the urine of a number of patients suffering from paroxysmal disorders of the cardiac mechanism who were receiving either quinidine sulphate or quinine hydrobromide in small doses over a period of several weeks. The test applied was precipitation of quinidine sulphate and quinine hydrobromide in distilled water and in urine by potassium mercuric iodide solution (Mayer's reagent).

In the present series of patients when 0.2 gram of quinidine sulphate was given, the alkaloid appeared in the urine within three hours and faint traces were always found at the end of twelve hours. In one patient, the urine showed a faintly positive reaction after twenty-three hours. An interesting exception occurred in a man suffering from advanced renal insufficiency; the blood urea nitrogen was 52 grams; there was no demonstrable passive congestion or edema; after 0.2 gram of quinidine sulphate was given, there was none in the urine obtained four hours later and the night urine was only faintly positive for the alkaloid; the urine at 9 o'clock the next morning was negative for alkaloid even in acid solution.

When patients were given 0.6 gram of quinidine sulphate or one gram of quinine hydrobromide daily in three doses all specimens of urine showed the presence of alkaloid. Certain patients suffering from paroxysmal auricular fibrillation have been helped by such quantities of these drugs but the presence of alkaloid in the urine bore no relation to therapeutic effects. Quinidine excretion is doubtless influenced by a number of factors, individual variation, diuresis, renal permeability for substances other than water and muscular effort.

Kissane, R. W.: Area of the Body Surface and Measurements of the Normal Heart in Children. Arch. Int. Med. **45**: 241, 1930.

In a previous report the necessity of finding a variable that has a close correlation with the size of the heart was emphasized and the area of the body surface was suggested because it includes other variables such as height, weight, age, sex, and diameter of the chest when persons of ideal weight are used as a standard. The present paper reports the determination of the size of the heart for an area of body surface of less than 1.5 square meters, 100 children between the ages of three and fourteen years with normal hearts and electrocardiograms being measured.

Height and weight without clothing were obtained in each case. Roentgenograms were made at a distance of six feet and measured for the transverse diameter of the heart and the diameter of the chest. The cases were classified as to their relation to ideal weight for a given height and age, the table of Woodbury being used for subjects under five years of age and the table of Baldwin and Wood for those above this age. For the determination of the area of body surface, the table of Benedict and Talbot gave the best results.

The author believes that cases of ideal weight for height should be used in the estimation of the measurements of normal hearts since cases of over or under

ideal weight for height have an antagonistic influence on the close correlation of the area of body surface with the mean transverse diameter of the heart.

In this series of children the mean transverse diameter of the hearts in girls was smaller than that in boys at any age. The area of body surface has the same close correlation to the size of the heart in children as in adults.

Increase in the weight of children as a group increases the range from the mean transverse diameter of the heart with the area of body surface as a variable.

Duke, W. W.: Heat and Effort Sensitiveness, Cold Sensitiveness. Arch. Int. Med. 45: 207, 1930.

In this paper the author enumerates a series of relatively common illnesses many of them serious which are caused rather frequently, he believes, by a disorder in the heat regulating mechanism. The illnesses include heat prostration, symptoms of effort syndrome, noninfectious coryza, asthma, urticaria, dermatoses and other miscellaneous ailments to be mentioned. They are commonly diagnosed neurasthenia, psychasthenia, allergy, atopy, vagotonia and eczema. The patients are hypersusceptible to infection during their reaction to heat or cold, especially infection in the nasorespiratory tract and for this reason their disorders are often classed with the infections.

The author discusses our present knowledge concerning the heat regulating mechanism of the body and the relationship of the body to outside temperature conditions and changes. He discusses the manifestations of typical heat and cold sensitiveness and the process of acclimation and declimation. He also discusses the relationship of heat and cold sensitiveness to infection, to atopy and to histamine-like bodies that have been described by Lewis, Eustis and Lewis and Vaughn.

The relationship that rheumatic fever has to climatic conditions and changes has been known for a long time. Many of the ideas discussed in this paper by the author might find some application to the occurrence of rheumatic fever in susceptible individuals. The part played by dampness, by heat and by light in the etiology of rheumatic fever might thus be explained. That rheumatic subjects are suspectible to heat changes and to infection is well known. The idea included in this paper is an important contribution to the present discussion as to the nature and etiology of rheumatic fever.

Levine, Samuel A., Ernstene, A. Carlton, and Jacobson, Bernard M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris. With Observations on the Electrocardiographic Changes Following Injections of Epinephrine into Normal Subjects and into Patients with Angina Pectoris. Arch. Int. Med. 45: 191, 1930.

Epinephrine was administered subcutaneously in doses of 1 c.c. to 3 groups of persons: To one, a group of 11 with angina pectoris, a second of 10 of the same average age but without angina and a third of 10 normal young adults. In all but one patient with angina pectoris, typical pain resulted from the injection. In none of the control patients did this pain occur. Electrocardiographic studies showed that following the injection of epinephrine the T-wave in the anginal group increased slightly in amplitude while in the other two groups it showed a tendency to decrease. The increase in blood pressure and pulse rate was somewhat greater in the anginal group than in the others.

It is suggested that the production of anginal pain by the injection of epi-

nephrine may serve as a diagnostic test for angina pectoris. The test would not be applicable when the diagnosis is certain but rather in doubtful cases or when there are other possible explanations for the symptoms, such as gallstones or disease of the stomach or the duodenum.

Because epinephrine produces typical pain with great regularity in patients with angina pectoris, therapeutic use of the drug in such patients should be carried out with great caution.

Fullerton, Charles, and Harrop, George A., Jr.: The Cardiac Output in Hyperthyroidism. Bull. Johns Hopkins Hosp. 46: 203, 1930.

The authors have estimated the cardiac output by measuring the rate of absorption of nitrous oxide from the alveolar air into the blood. Eight carefully selected patients with typical manifestations of the disease without evidence of organic cardiac disease or of lung disease were studied. The clinical examination was confirmed by electrocardiographic studies and x-ray examination of the chest. The technic and apparatus were those employed by Marshall and Grollman. The determinations were done upon the patients as soon as possible after admission to the hospital and then at intervals during the course of their treatment. The first point to be noted is that under basal conditions where quiet and relaxation were realized as much as possible the increased pulse pressure usually reported in hyperthyroidism was not found. Surprisingly little difference also was found in the blood pressure before and after treatment even over prolonged periods.

Since the difference in blood pressure before and after treatment is very small, the difference in cardiac output should then be a direct measure of the increased cardiac work. They found a parallelism between the increase in the basal metabolism and the cardiac output per minute. They believe that the work of the heart is increased at least to this amount. The fairly close relation which exists between elevation of metabolism and cardiac output in hyperthyroidism strongly suggests that the level of the metabolism in the disease is a factor of the first importance in the regulation of the cardiac output per minute under basal conditions.

Johnson, Charles C.: The Salicylates. XIX. The Question of Acidosis Following the Administration of Salicylates. J. A. M. A. 94: 784, 1930.

The author has studied the effect of administration of readily absorbable salicylates in doses equivalent to full therapeutic doses, on the alkali reserve of the blood in rabbits and cats. He found that the administration of these salicylates caused a definite and general marked respiratory stimulation, though the hydrogen-ion concentration remained unchanged and there was no acetone demonstrable in the urine. These changes are best reconciled as the equivalent of a fixed acid acidosis, compensated by loss of carbon dioxide. Definite increases in blood lactate were correlated with significant decreases in alkali reserve and respiratory stimulation in four of eight cats receiving sodium salicylate in doses equivalent to the full therapeutic; the remaining four cats did not show evidences of acidosis, but in view of the respiratory and blood changes that occurred there was still a correlation between these functions. Various possibilities regarding the origin of the increases in the fixed acid occurring in salicyl medication are indicated.

The author believes that the use of bicarbonate together with salicylates in full therapeutic doses in rheumatic fever and also in the treatment of salicylate poisoning is rational on experimental grounds at least.

Strauss, Maurice B.: Paroxysmal Ventricular Tachycardia. Am. J. Med. Sc. **175**: 337, 1930.

The author reports two cases of paroxysmal ventricular tachycardia and reviews the literature briefly relating to sixty-three cases. No common single etiological factor could be discovered but 84 per cent of the cases occurred in patients suffering from organic heart disease and of these 60 per cent had been treated with digitalis prior to the onset of the tachycardia. In the absence of organic heart disease the prognosis of paroxysmal ventricular tachycardia is good.

The diagnosis at the bedside can usually be made from a slight irregularity frequently noted on auscultation which is found in tachycardia of ventricular origin not to be found in other forms. The quality of the first heart sound may perceptibly vary in different cycles. Vagal stimulation and ocular pressure are never effective in terminating a paroxysm of ventricular tachycardia. Positive diagnosis can only be made by the electrocardiograph.

Quinidin offers a valuable remedy with uniform success in ending the tachycardia.

Keefer, Chester S.: The Beriberi Heart. Arch. Int. Med. **45**: 1, 1930.

A group of 15 patients with beriberi were studied with particular reference to the cardiovascular system. It was clearly demonstrated that patients who developed cardiac insufficiency are those who have the least involvement of the nervous system. The author believes that when the peripheral nervous system becomes involved so as to produce paresis that the heart muscle is protected by the lack of activity to a degree that cardiac insufficiency either does not develop or remains slight. Whereas, if the heart muscle becomes involved first then signs of cardiac insufficiency predominate.

The hypotheses that have been advanced in explanation of the mechanism in heart failure in this disease are reviewed and the mechanism discussed. He believes that the right heart is involved to a very great extent. This can be demonstrated by electrocardiographic and roentgenographic examinations. The process in the heart muscle consists of edema and injury to the contractile heart elements. The deficiency of Vitamine B probably plays an important part in this change. The importance of diet and exercise in the management of this form of heart disease is emphasized.

Werner, Walter I: Tuberculous Pericarditis. Am. Rev. Tuberc. **21**: 202, 1930.

Of 67 tuberculous patients autopsied, 4 or 5.9 per cent had tuberculous pericarditis. The author reports 3 of these cases, two of which were recognized clinically. He points out that the symptoms of tuberculous pericarditis are very obscure and the diagnosis depends upon a general survey of the case with reference to the probability of tuberculous infection. In the acute miliary form, the diagnosis is generally impossible, the pericardial reaction being too slight to attract attention. In the subacute form it may also be overlooked. It is often revealed by special symptoms especially pain and x-ray examination. Occasionally the pericarditis is associated effusion. The fluid may be hemorrhagic or purulent. Tubercle bacilli may be recovered from this fluid.

Wiggers, Carl J.: Studies of Ventricular Fibrillation Caused by Electric Shock. Am. J. Physiol. **92**: 223, 1930.

The author has studied ventricular fibrillation caused by electric shock particularly the question of the revival of the heart from such fibrillation by successful use of potassium and calcium salts. He discusses fully the reported in-

stances of recovery from fibrillation and believes that they occur under conditions unattainable in the intact heart or that the recovery resulted from the use of methods not applicable to the intact heart or that the condition was not proven ventricular fibrillation produced by electric currents.

He points out that it is important to demonstrate that cessation of ventricular activity exists at the time the measures directed toward recovery are instituted. Under these conditions there may be some doubt that revival of the heart itself is possible since fibrillation lasts as a rule from fifteen to fifty minutes, the average duration being twenty-four minutes. Under these conditions anemia of the brain may have existed so long as to make recovery of the whole body impossible.

He believes that potassium-calcium perfusions may be used either by coronary perfusion, by direct injection into the ventricular muscle, or by injection within the ventricular cavity. After the cessation of fibrillation by the use of potassium perfusion a coordinated beat may be restored by similar perfusion of an isotonic solution containing an excess of calcium.

Coronary perfusion demands the sacrifice and ligation of a carotid artery under aseptic conditions, a performance requiring rather elaborate perfusion apparatus and therefore is frequently not adaptable to practical needs. Furthermore, such perfusion is apt to result in a filling up of the dead spaces of the circulation rather than an introduction of the fluid within the ventricular cavity. Injection into the ventricular cavities of the solution causes a resumption of a coordinated beat provided the fluid is pumped through the coronary vessels by massage. Without massage it is ineffective. This is particularly true of the calcium solution. No chemical substitute for massage has been found as a result of extensive experimentation.

The author concludes that while the methods offer some promise of success when applied promptly to patients after electric shock, hope of resuscitation in man by methods so far devised is necessarily limited to cases in which the surgical possibilities and circumstances approximate those obtainable in laboratory animals. The fact that cardiac massage is required is a serious drawback to the practical use of the intracardiac method in the field.

Book Reviews

TRAITÉ D'ELECTROCARDIOGRAPHIE CLINIQUE. By Paul Veil and Juan Codina-Altes. G. Doin et Cie, Paris.

The authors of this work are pupils of Gallavardin, eminent French cardiologist, who has written an excellent preface emphasizing the importance of the electrocardiographic method. Cluzet, Bret, and Bard, all of Lyon, have also contributed; the first, a chapter on the origin of the electrical currents produced by the cardiac muscle; the second, a chapter on cardiac hypertrophy studied by the method of Müller; and the last, a section upon the influence of the intracardiac pressure upon the cardiac mechanism, normal and abnormal. Rothberger of Vienna has given an excellent account of his ideas concerning parasystole.

The scope of the work is similar to that of *The Mechanism of the Heart Beat* by Lewis and *Unregelmässige Herztätigkeit* by Wenckebach and Winterberg. On the whole it is less satisfactory than either of these monographs, although it is an excellent discussion of the subject and presents a different viewpoint. Unfortunately a large proportion of the figures, of which there are a great many, are so poorly reproduced that they are almost, if not entirely, illegible. In a few instances the figures are upside down, and one or two of the legends obviously belong to some figure other than the one which they accompany. One or two figures taken from the works of others are attributed to the wrong source.

The book contains no bibliography. In a few instances specific reference to the work of others is given; usually, however, only the name of the authority whose work or opinion is quoted is given. Consequently it is impossible to find the original contributions which are referred to.

The authors attribute a much greater rôle to the intrinsic cardiac nerves than do most cardiologists in this country. They also show a very pronounced tendency to divide and subdivide the disturbances of the heart beat into a great many clinical syndromes, not all of which are well defined. As an example we may refer to their discussion of paroxysmal tachycardia. They recognize three chief types:

I. *Tachycardies paroxystiques du type Bouveret.* This is the classical form of the disorder. The authors believe that it is not due to a succession of extrasystoles, and that it is in no way related to extrasystolic arrhythmia. They state that when extrasystoles do occur at the beginning or end of an attack, or when they occur between attacks, they are never of the same form as the beats of the paroxysm itself, and consequently do not arise at the same point and are not generated by the same mechanism. They distinguish between long attacks which occur at relatively long intervals, and very short attacks which occur with great frequency. They refer to the latter condition as "Tachycardie paroxystique à centre excitable."

II. *Tachycardies paroxystiques d'origine extrasystolique.* The authors regard this type as entirely different from that described above. It is made up of a succession of extrasystoles. When the attacks are short and numerous; that is, when relatively few extrasystoles occur in succession, each group of extrasystoles being separated from the group which precedes and that which follows it by one or more normal beats, the condition is referred to as "*extrasystoles en salves.*" Very long attacks which they regard as relatively rare are spoken of as "*extrasystoles massées.*"

III. *Tachycardies anormales.* This group is poorly defined; it contains those cases which do not seem to the authors to belong to either of the two previous groups. It is divided into two divisions:

A. Non-terminal. Under this heading a number of examples of tachycardia, no two of which are alike, except that all are benign, are discussed.

B. Terminal. These cases are mostly examples of ventricular tachycardia in which the ventricular complexes varied greatly in form.

The same tendency to recognize a great variety of syndromes is found in the discussion of atrio-ventricular rhythm and of sinus arrhythmia. The authors believe that true atrio-ventricular rhythm is usually irregular. They are particularly interested in those cases in which there is complete atrio-ventricular dissociation, but in which auricles and ventricles are contracting at the same rate, or nearly the same rate, the former responding to the sinus node, the latter to the A-V node. To this condition they give the name "*Dissociation isorhythmique,*" of which they distinguish several varieties. A study of this condition as well as other observations have led the authors to believe that the intrinsic cardiac nerves act as a regulatory apparatus which coördinates the various impulse-producing centers of the special tissues. Some disturbances of the heart are regarded as due to disturbances of this coördinating mechanism; others as due to its normal regulating function. They speak, for instance, of non-compensatory arrhythmias; benign extrasystoles, ordinary paroxysmal tachycardia, which are due to hyperexcitability of ectopic centers produced by hyperactivity of the sympathetic nerves. In this case the coördinating mechanism is disturbed. Certain extrasystoles, ventricular escape, certain types of nodal rhythm, certain types of bigeminy, on the other hand, are regarded as compensatory phenomena, due to an attempt on the part of the nervous regulatory mechanism to maintain a normal heart rate. To the reviewer these ideas seem too speculative for general acceptance in the present state of our knowledge.

As regards the form of the electrocardiogram, the authors are much more conservative. They do not believe that the form of the ventricular complex is of any value in the diagnosis of valvular lesions and regard the broad deformed auricular complex of mitral stenosis as the sole change in the form of the electrocardiogram which can be considered at all characteristic of a valvular defect. Their views of the T-deflection, and of curves of small amplitude do not differ materially from those current in America. They regard preponderance curves as the result of intraventricular conduction defects.

F. U. W.

THE CLINICAL ASPECTS OF VENOUS PRESSURE. By J. A. E. Eyster. New York, The Macmillan Company, 1929.

In this small volume Dr. Eyster gives a résumé of the literature and of his own work on the subject of venous pressure. He discusses the mechanics of venous pressure and the relation of increased pressure to the symptoms of cardiac failure, the methods of determining venous pressure and the findings in normal individuals, in patients with cardiac decompensation and in conditions other than cardiac failure. Because increase in venous pressure is an important factor underlying the symptoms of cardiac failure and an index of such failure and because such increase can be determined accurately and easily, the author feels that venous pressure determinations should receive more attention, and in this book he writes especially for the clinician.

E. H.

LES ANÉVRYSMES ARTÉRIO-VEINEUX. By Raymond Grégoire, Professor of the Paris Faculty of Medicine and Surgeon to Tenon Hospital. Baillière, Paris, 1930. Pp. 214 (with 5 plates and 8 figures).

Experimental work and observations made during the War have enlarged our knowledge of arterio-venous aneurysms. Professor Grégoire, by study and experience, is specially qualified to discuss this subject, and in this monograph he emphasizes the pathological physiology and presents his own ideas and technique of operative treatment. He illustrates his text with well-chosen drawings and case reports, and discusses the subject under the headings of causes, pathological anatomy, physical signs and their physiological meaning, prognosis, diagnosis and treatment. The chapters on treatment and on aneurysms in particular locations fill the second half of the book and should be very useful.

E. H.

THE VOLUME OF THE BLOOD AND PLASMA IN HEALTH AND DISEASE. By Leonard G. Rowntree, and George E. Brown with the Technical Assistance of Grace M. Roth. Philadelphia, 1929, W. B. Saunders Company.

This little book is timely and welcome. It presents in condensed form the available knowledge concerning the variations in blood and plasma volume found in normal individuals and in many disease conditions, and represents the accumulated results of a number of years of patient careful work. The need of supplementing our routine blood examinations by some method of measuring the total volume of the blood must long have been felt by every thoughtful clinician, but no such method has yet come into general use. The authors are convinced that the dye method, introduced by Keith, Rowntree and Geraghty fifteen years ago, has stood the test of time and that it is a "practical procedure of great clinical importance." It seems probable that the appearance of this book will do much to popularize the use of the dye method and that it will attract attention to the importance, in any clinical study of the blood, of a variable which hitherto has received much less consideration than it deserves.

L. A. C.

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